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Title of Dissertation: "Neuropsychological Construct Structure of a Brief Computerized Neuropsychological Battery: Windows Spaceflight Cognitive Assessment Tool (WinSCAT)"

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Doctor of Philosophy Degree
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ABSTRACT

Title of Thesis: "Neuropsychological Construct Structure of a Brief Computerized Neuropsychological Battery: Windows Spaceflight Cognitive Assessment Tool (WinSCAT)"

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Computerized performance assessment of neurocognitive functioning has increased tremendously over the past several years. However, little is known about how well these measures assess neurocognitive constructs they are purported to evaluate, especially in healthy, non-clinical populations. The Windows Spaceflight Cognitive Assessment Tool (WinSCAT) is a five-subtest battery derived from the larger Automated Neuropsychological Assessment Metrics (ANAM) computerized battery for use in evaluation and assessment of spaceflight crew members during space missions. The WinSCAT subtests also have been applied for assessing neurocognitive functioning in clinical populations. Findings indicate the WinSCAT subtests evaluate the cognitive domains of attention, executive functioning, memory, and possibly visuospatial processing. To determine the cognitive content structure of the WinSCAT in healthy non-clinical samples, two studies were performed based on both archival and prospectively-collected data sets. A battery of widely used, traditional clinical neuropsychological tests was administered with the computerized WinSCAT. Bivariate correlation and multiple regression data analyses were utilized to evaluate the extent to which the WinSCAT subtests were associated with specifically-hypothesized cognitive

domains. Statistically significant demographic, general ability, and motor functioning variables were covaried to control for their potentially confounding contributions to relationships between the traditional and computerized testing measures. The WinSCAT tasks in the first (archival) study were found to predict performance on traditionally-derived index scores of attention, executive functioning, and memory. In the prospectively-collected data for study 2, the WinSCAT tasks were found to predict performance on traditionally-derived scores of executive functioning, memory, and visuospatial processing. The combined results across the two studies overall support the four-domain structure of the WinSCAT, with some differences in the specific domains supported in the separate studies. The neuropsychological domain of memory was supported in both studies, whereas the domains of attention, executive functioning, and visuospatial processing were supported in one of the two studies. Differences between the samples are believed to have contributed to the failure to obtain full support for all four domains across both studies. These results have implications for the appropriateness of future use of the WinSCAT to evaluate neurocognitive functioning for application with healthy and clinical samples.

Neuropsychological Construct Structure

of a Brief Computerized Neuropsychological Battery:

Windows Spaceflight Cognitive Assessment Tool (WinSCAT)

By

John R. Ashburn, Jr.

Doctoral Dissertation submitted to the Faculty of the
Department of Medical and Clinical Psychology
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On tops of mountains, as everywhere to hopeful souls, it is always morning. – Thoreau

The past several years have indeed been akin to climbing a mountain and, as is the case for most of life, the tremendous effort expended along this journey is proportional to the great sense of satisfaction I enjoy. Keeping with the metaphor, this journey has also required the efforts of a great many people along the way, who I take this opportunity to acknowledge.

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weaknesses, however, were mine upon entering this field, and thus remain strictly my own.

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INTRODUCTION

Neuropsychological testing has been broadly defined as the administration of standardized tests that are reliable and valid with respect to assessing specific (or suspected) impairments in brain functioning (Lezak, 1995). Referrals for neuropsychological assessment often involve testing for the potential contribution of the central nervous system (CNS) in symptom manifestation. One study indicated that 30% of referrals to psychologists in general neuropsychiatric settings specifically requested information related to CNS involvement (Craig, 1979). Traditional neuropsychological testing provides an established manner by which to evaluate an individual's behavior across a wide range of variables (e.g., those involving cognition and affect). Clinically, the patterns of that individual's performance across those variables are compared to specific patterns that have been identified in distinct clinical populations with known neurological conditions. The neurocognitive functions that are evaluated are generally categorized in terms of the cognitive domains that have been associated with distinct neural systems. For example, a left hemisphere temporo-parietal stroke commonly results in performance deficits in the cognitive domain of language, with relatively preserved general visuospatial functioning, and a right hemisphere parietal stroke is likely to produce deficits in the domains of attention and visuospatial perception, with relatively intact language ability (Andrewes, 2001).

Although traditional neuropsychological testing has a great deal of clinical utility and provides much useful information about an individual's specific strengths and weaknesses across different cognitive domains, it has inherent limitations. In their comprehensive review of computerized assessment in neuropsychology, Kane and Kay

(1992) summarized the relative deficits of traditional neuropsychological testing. These limitations include: an emphasis on one-time test administration to provide a "snapshot" of functioning, a focus on comparison with peers rather than within-individual normalization, and a lack of emphasis on functional performance measurement. Other limitations of traditional neuropsychological assessment include the large time needed for testing broad-based cognitive domains of function and for scoring and interpreting the paper-and-pencil administered tests, combined with the large expense incurred with this process, and lengthy delays in providing feedback.

The advent and evolution of computerized assessment tools for neuropsychology over the last 25 years has greatly expanded the options of the neuropsychologist. In contrast to traditional neuropsychological assessment methods, advantages offered by computerized neuropsychological assessment include improved standardization, precise stimulus control, multidimensionality of response components, and improved cost efficiency (Kane & Kay, 1992). Computerized assessment tools also provide a means for effective within-subject, repeated-measure assessment of functioning and, assuming that they are appropriately normalized, for functioning alone as an effective, repeatable neuropsychological screening tool (Horst & Kay, 1988).

The evolution of computerized neuropsychological assessment tools has been extremely rapid and coincides with the rapid development of available technologies (e.g., hardware capacity, software integration). The development of specific computerized assessment applications has been largely guided by clinical intuition regarding the face-valid similarities of the cognitive domains measured by computerized and traditional assessment tools (e.g., the traditional Wisconsin Card Sort Test [WCST] and the

computerized WCST). As such, the construct validity of many computerized neuropsychological assessment measures remains questionable (Kabat, Kane, Jefferson, & DiPino, 2001). Few published studies have directly assessed the comparability of cognitive domains measured by traditional neuropsychological testing and computerized neuropsychological testing within the same subjects. The published studies that have conducted such comparisons have examined these relationships within clinical samples. Such samples have significant variability across different domains of cognitive functioning that are related to the nature and location of neurological insult. Findings from clinical studies comparing traditional and computerized assessment have identified three to four shared factors associated with the cognitive domains of attention, executive functioning, learning and memory, and visuospatial processing (Kabat et al., 2001). However, given the dearth of literature comparing the relationship between traditional and computerized assessment tests and methods in healthy, neurologically-normal individuals (as contrasted with clinical populations), this relationship remains unclear in a non-clinical population. It is important to examine these methodologies with normal healthy subjects, both to determine the psychometric comparability of these different assessment approaches and for extending the application of computerized assessment technology in non-clinical settings.

The scope of this doctoral dissertation research project involves two different but conceptually-related studies. Study 1 consists of the comparative analyses of existing traditional and computerized neuropsychological data collected as part of two research protocols ("Randomized, Placebo-Controlled Study to assess the Safety of Combination Preventative Treatment with Pyridostigmine, DEET, and Permethrin" [protocol

#G183LZ, Dr. Michael Roy, PI] and "Tyrosine Effects on Physical and Cognitive Performance" [protocol #G19190, Dr. Patricia Deuster, PI]). The combined data pool from these two protocols consists of 99 physically and psychiatrically healthy adult subjects. A small number of preliminary comparisons between the traditional and the computerized data have been completed; however, none of the findings from those preliminary analyses have been published. The traditional neuropsychological testing data that were collected were designed to provide information on an individual's general intellectual and motor skills and functioning in eight broad-based cognitive domains including: attention, language expression, verbal learning, verbal memory, visuospatial skill, visual memory, problem solving/reasoning, and executive functioning skills. The specific measures that were used included: the Shipley Institute of Living Scale, the Grooved Pegboard Test, the California Verbal Learning Test (CVLT), the Rey-Osterrieth Complex Figure Test (ROCF), the Trail Making Test (TMT) Parts A and B, the Stroop Color-Word Interference Test, the Controlled Oral Word Association Test (COWAT), Wechsler Memory Scale III (WMS-III) Logical Memory (LM) and Family Pictures (FP) subtests, and seven Wechsler Adult Intelligence Scale – III (WAIS-III) subtests (Picture Completion, Information, Similarities, Matrix Reasoning, Symbol Search, Letter-Number Sequencing, and Digit Span). The computerized data that were collected in the same two protocols were derived from the Spaceflight Cognitive Assessment Tool for Windows (WinSCAT), a five-test subset of the larger automated neuropsychological assessment metrics (ANAM) computerized neuropsychological testing library. The WinSCAT tests are code substitution, running memory, mathematical processing, match-to-sample, and delayed code substitution (memory).

Study 2 is a comparison of traditional and computerized neuropsychological measures in a newly collected data sample consisting of 75 physically and psychiatrically healthy adults. The traditional neuropsychological measures used in study 2 were designed to specifically evaluate the four primary cognitive domains that have been found to be related to the WinSCAT subtests in published studies examining clinical samples (Bleiberg, Kane, Reeves, Garmoe, & Halpern, 2000; Kabat et al., 2001) and in preliminary exploratory factor analyses (Retzlaff & Vanderploeg, 1999). These cognitive domains are: attention, executive functioning, memory, and visuospatial processing. A minimum of three traditional neuropsychological tests that have been empirically established as measuring shared functioning in each of these domains were administered for comparison with the WinSCAT tests. In addition, the subjects' general intellectual functioning and simple motor speed were evaluated for use as covariates. The specific measures that were used in this data collection study included: the Shipley Institute of Living Scale, the Grooved Pegboard Test, the Rey Auditory Verbal Learning Test (RAVLT), the TMT Parts A and B, the Stroop Color-Word Interference Test, the Paced Auditory Serial Addition Task (PASAT), one WMS - III subtest (Verbal Paired Associates), six WAIS - III subtests (Block Design, Matrix Reasoning, Digit Symbol/Coding, Symbol Search, Letter-Number Sequencing, and Digit Span), and one subtest from the Wechsler Memory Scale –Revised (WMS-R; Figural Memory). As in study 1, for study 2 the computerized testing battery consisted of the WinSCAT battery of tests.

To provide background for the present research, the history and development of the field of neuropsychology and neuropsychological assessment is reviewed. The

historic nature and purpose of the traditional neuropsychological testing approach is discussed, with an emphasis on the evolution and current challenges within the discipline of clinical neuropsychology. The emergence of computerized assessment approaches in clinical neuropsychology is then examined. Particular emphasis is placed on the expectations regarding the advantages and disadvantages offered by computerized approaches in general, with specific comparison of the differential strengths and weaknesses afforded by computer and traditional neuropsychological testing methods. The literature addressing the sensitivity of computer-based measures for use in clinical neuropsychological assessment over the past decade is reviewed in terms of general features as well as the findings in specific clinical populations that have been evaluated with computerized assessment procedures. Continued issues and methodological concerns associated with computerized assessment methodologies in neuropsychology in the 21st century is summarized. The review concludes with a summary of the findings related to neuropsychological assessment with the WinSCAT battery in a variety of published studies. Ongoing interest in the WinSCAT battery has been generated due to its regular use in several high-visibility arenas, including with NASA astronauts (Kane, Flynn, Vanderploeg, Retzlaff, Moore, et al., 1999). Emphasis is placed on the strengths and weaknesses of the WinSCAT in relation to the general continued limitations associated with computerized testing and means by which the WinSCAT battery addresses some of those limitations. This discussion is followed by a summary of the improvements that have occurred in the computerized assessment arena as well as an examination of the continued unanswered questions in the published literature. The paper then introduces the purpose and specific aims of this project. Next, the study

rationale, hypotheses, methodology, and data analyses are presented, followed by the results and discussion of findings for each study, a general discussion of the combined studies' results, and the overall conclusions.

Review of the Literature

Historical Roots and Issues in Neuropsychology

Neuropsychology is a scientific discipline that examines the relationships between the central nervous system and behavior in both basic research (experimental neuropsychology) and clinical applications (clinical neuropsychology) (Luria, 1973). One means for examining this relationship has been based on the deficit model, in which behavioral changes are examined in relation to injury to specific brain regions or neural systems. The historic development of neuropsychology has roots dating to ancient history. The first documented instance of localization of cortical function was dated from approximately the seventeenth century BC (Stuss & Levine, 2002). The beginnings of neuropsychology as a formal discipline are usually dated to the nineteenth century with the findings of Broca (1863) and Wernicke (1874) on brain areas impacting speech (Kolb & Whishaw, 1996). However, the term "neuropsychology" was not used until 1913, and it did not enter the psychology community nomenclature until over 20 years later, in 1936 (Bruce, 1985). The formation of neuropsychological assessment as a systematic discipline is usually dated to the 1940's (Lezak, 1988; Groth-Marnat, 1999). The temporal relationship of the rapid development of the field of clinical neuropsychology and World War II was not a coincidence. Instead, the brain injuries incurred during that war, and the rehabilitation programs that naturally followed, helped create the demand for

comprehensive neuropsychology services and programs. Additionally, during this timeframe, several controversies that had split the field of clinical neuropsychology were being actively addressed and reconciled.

One important controversy within the development of neuropsychology involved those who believed in the holistic function of the brain versus those who believed in the localized function of the brain (Meier, 1992). The former believed that all brain functions coexisted diffusely in the cerebral cortex (equipotentiality), while the latter believed that particular localized regions of the cortex corresponded with specific cognitive and behavioral functions (e.g., speech production). Well-known figures in neuropsychology lined up on both sides of the localization debate. Names commonly associated with the holistic doctrine were Flourens, Goltz, and Lashley, while the localization doctrine was supported by Broca, Wernicke, Fritsch, and Hitzig. Both sides in this debate marshaled evidence from the empirical literature. For example, the whole brain supporters could point to animal research findings of Flourens to support their position. He found that loss of intellectual faculties correlated with the extent of cortical ablation, largely independent of the location of the ablated tissue (Flourens, 1824). In contrast, the work of Broca indicated a specific cortical brain region in the left posterior inferior frontal lobe that was responsible for the production of speech (Broca, 1861). The publication of *The Organization of Behavior: A Neuropsychological Theory* (Hebb, 1949), which incorporated the findings on the functional hierarchy of the nervous system provided by the early twentieth century English neurologist, John Hughlings-Jackson, provided the first integration and synthesis of the two schools of neuropsychology that

differentially emphasized the localizationist and equipotentiality positions (Kolb & Whishaw, 1996).

A. R. Luria, the Russian psychologist and neurologist, later elaborated and extended this synthesis (Luria, 1966). Through his extensive clinical study of the consequences of brain injuries during World War II, he formulated the concept of functional neural systems and their identification through a targeted combination of qualitative and quantitative testing (Luria, 1948; Luria, 1970). This assessment methodology lent itself to the analysis of symptom clusters for estimating regional localization associated with impaired cortical areas (".....a detailed qualification of the symptom observed", p. 35) (Luria, 1973). The idea of functional systems allowed for redundancy and interdependencies of functions at varying neural levels, and explained findings related to neuropsychological deficiencies and recoveries that were unexplainable with either the localizationist or equipotentiality positions alone (Meier, 1992).

In addition to the localization/equipotentiality debate that was integrated and reconciled by Hebb and Luria, another classic controversy within the clinical neuropsychology field contrasted the idiographic, individual differences approach with the nomothetic, standardized group approach to assessment and interpretation of testing results. This latter issue derives somewhat paradoxically from the diverse roots of neuropsychological assessment in the disciplines of both psychology and neurology. During the 1940's and 1950's, American neuropsychology underwent a change (reflecting the changing Zeitgeist in American psychology) to a more atheoretical, empirical, actuarially-driven methodology than had existed previously (for a review see

Hunt, 1993). With this nomothetic approach, individual patient data could be compared with normative data of various clinical groups to arrive at a statistically-probable diagnosis. Simultaneously, in Russia, A. R. Luria (trained in both neurology and psychoanalysis) was developing a neuropsychological approach that was clinically-driven, theoretical, and based on individual case-study findings (Lezak, 1995). This idiographic approach sacrificed standardization of measurement (by choosing neuropsychological tests and procedures based on the individual patient's circumstances) for a more comprehensive and qualitative evaluation of the patient's individual manifestation of cognitive and behavioral difficulties.

A current synthesis of these different approaches to assessment is captured by an approach that has been termed "process-oriented" and which combines the strengths of both the individual difference model and the nomothetic methodologies for understanding disordered behavior (i.e., the Kaplan Boston Process approach; White & Rose, 1997). A process-oriented approach in neuropsychology utilizes a set of core neuropsychological tests that are standardized and empirically validated for nomothetic comparison, in combination with situationally-specific measures that allow examination of the individual patient's unique approach to completing the tests (Mapou, 1995). This methodology is flexible and allows for both actuarial and clinical interpretation of clinical data. Additionally, this method allows for the analysis of performance in specific cognitive domains of functioning (e.g., attention) using a variety of tests from different batteries.

The increasing recognition of a role for process-oriented approaches in neuropsychological assessment contributed to the expanded methodologies available for conducting neuropsychological evaluations. These included strict battery-based

approaches, in which all tests were administered as a standardized battery and compared with normative data from the same battery (e.g., Halstead-Reitan Neuropsychological Test Battery) and more flexible approaches in which specific tests were selected based on the individual patient's presenting problem, neurological condition, and referral need (Kane, 1991). Specific emphasis was placed on the importance of continued and ongoing assessment of "the nature of neuropsychological measures and the abilities they assess" (Kane, 1991, p. 281).

Traditional Neuropsychological Assessment: Clinical applications and methods

As a discipline, clinical neuropsychology has been defined as "the applied science concerned with the behavioral expression of brain dysfunction" (Lezak, 1995, p. 7). Through its assessment methodologies and approaches, clinical neuropsychology has the potential to assist in helping answer a wide range of neurological and psychological questions. For mental health providers, clinical neuropsychology can help identify and meaningfully classify those individuals with underlying neurological disorders. For neurologists and neurosurgeons, clinical neuropsychology can be used to assist in diagnosis, treatment planning, and disease course evaluation. Various patient populations are thought of as often requiring neuropsychological assessment including: those with traumatic brain injury (TBI), those abusing substances, those exposed to neurotoxic substances, and elderly populations.

The traditional clinical neuropsychological assessment methodology has typically been associated with one of two broad approaches: the pathognomonic sign approach and the quantitative cutoff score approach (Groth-Marnat, 1999). The pathognomonic sign approach is a dichotomous approach, using the existence of a specific assessment finding

as de facto evidence of brain damage. For example, findings of an aphasia (an acquired impairment of the ability to use or comprehend words) in a neuropsychological evaluation is considered a pathognomonic sign of brain damage. In contrast, in the quantitative cutoff sign approach, a specific assessment result (e.g., a test score) would be classified as falling into either an impaired or normal range.

Consistent with the advancing technologies, world-wide communication capabilities and increased knowledge, the focus of clinical neuropsychology has changed considerably over time. Early in the history of neuropsychology, (e.g., in the 1940's) the primary role of neuropsychological assessment was diagnostic and the goal was to differentiate between organic and functional causes of a patient's behavioral or emotional difficulties (Lezak, 1995; Mapou & Spector, 1995). However, this distinction between organic and functional etiologies has since been challenged (Leonberger, 1989), based on the underlying assumptions of such a dichotomy, for example, that biological and psychosocial factors act on an individual in isolation. In addition, increased technological improvements gradually reduced the need for neuropsychological identification of a probable brain lesion. As a result, clinical neuropsychology moved away from measurement solely for determining presence or absence of brain injury towards an additional emphasis on application of findings to understand the effects of neurological damage and to improve performance in clinically normal populations (Ponsford, 1987).

Computerized Assessment: Early Developments

An interest in computerized psychological assessment dates to the 1950's, although at that time the focus of this interest was in the academic and research arenas,

especially given that the available technology was still in its infancy (Schatz & Browndyke, 2002). With the dramatic evolution of computer technologies from the 1950's to the present, technological limitations have become increasingly minimized. Despite these advances, the use of computers in clinical neuropsychology has been found to lag behind the level of technical integration into other professions (Schatz & Browndyke, 1999). Several core issues relating to computerized neuropsychological assessment have existed since its initial evolution and remain relevant today. These issues include construct validity, relative advantages and disadvantages, and data storage/ethical considerations.

Early computerized assessment tools tended to be computerized versions of traditional neuropsychological paper and pencil tests. The most prominent example may be the Wechsler Adult Intelligence Scale (WAIS), first automated in 1969 (Elwood & Griffin, 1972), Other early examples include the Category Test (automated in 1975), the Peabody Picture Vocabulary Test (PPVT), and the Wisconsin Card Sort Test (WCST) (Schatz & Browndyke, 2002). While the ease of administration, improved reliability, and increases in the speed of scoring and interpretation of these measures provided significant improvements over their traditionally administered counterparts, utilization of the computerized versions of these measures is less than would be expected based on these advantages (Kane & Kay, 1997). One reason that has been cited for this apparent underutilization relates to the lack of psychometric consistency between the traditional and computerized versions of a test. For example, the many computerized versions of the WCST have been found to have different psychometric characteristics than the traditionally administered version of the test (Fortuny & Heaton, 1996). Whether this

difference in psychometrics results from the administration medium per se (e.g., computer-based administration engendering a faster rather than more accurate response), rather than some other factor(s), remains unknown.

Along with computerized versions of specific traditional neuropsychological tests, another set of computerized tests that have evolved are more general test batteries (Kane & Kay, 1992). These applications have elements of traditional tests (e.g., versions of the WAIS Digit Span subtest) that can be combined with other measures to evaluate specific cognitive domains. For example, the MicroCog Assessment of Cognitive Functioning (Powell, Kaplin, Whitla, Weintraub, Catlin, et al., 1993; Lopez, Sumerall, & Ryan, 2002), a computerized neuropsychological test battery, contains measures for five cognitive domains (attention, memory, reasoning, spatial processing, and reaction time), where each domain contains a number of subtests. A further evolution of such multiple cognitive domain measures is categorized as performance assessment tests (Kane & Kay, 1992). These types of computerized test batteries (e.g., the Automated Neuropsychological Assessment Metrics [ANAM]) measure various cognitive domains of function but, additionally, are designed for repeated-measure assessment of subtle changes in cognitive functioning. Hence, the tests are not computerized versions of traditionally-delivered tests (e.g., the computerized Digit Span test) but are substantially different measures. However, like traditional neuropsychological tests, computerized performance assessment tests are designed to measure functioning in various cognitive domains.

Potential applications for performance assessment tests include cases where serial (i.e., repeated-measure and within-subject) assessment is indicated. Eight common areas

of serial assessment include: 1) evaluating the effects of environmental stress, 2) assessing the effects of toxic substances, 3) assessing the effects of maturation, 4) monitoring disease progression and recovery for injury, 5) assessing the effects of medications on performance, 6) assessing the effects of medical and surgical interventions, 7) evaluating training effects and the effects of cognitive rehabilitation, and 8) assessing alterations of equipment design on performance (Kane & Kay, 1992). The utility of computerized performance assessment tests is readily apparent in instances when these factors are present. However, the lack of empirical literature relating performance assessment tests to traditional neuropsychological tests, and the underlying cognitive domains they purport to measure, remains a major stumbling block to increased implementation of such measures (Letz, 2003).

Traditional versus Computerized Assessment: Advantages and Disadvantages

The most comprehensive general review of computerized neuropsychological tests to date is represented by the work of Kane and Kay (1992) (an updated review specifically focusing on the WinSCAT was published by Kane, Short, Sipes, & Flynn, 2005). They summarized the relative advantages and disadvantages of traditional (termed "neuropsychological assessment") and computerized (termed "performance assessment") testing methods. Relative advantages of traditional neuropsychological assessment are evident in cases where a one-time test administration to measure functioning is indicated, where a focus on the comparison with peer-based norms is desired, and where sensitivity to localization of cortical insult is indicated (e.g., disease identification). Relative advantages of using computerized neuropsychological performance assessment tools are seen in cases when repeated-measures administration is

desired (e.g., serial assessment cases), multidimensionality of response elements is desired (e.g., response speed, accuracy, and variability in both over time), and rapid administration, scoring, and feedback is required.

Contemporary Challenges in Computerized Assessment

The relative advantages and disadvantages of computerized neuropsychological measures exist in parallel with several more fundamental issues in the field of computerized neuropsychological assessment. Some of these issues, especially those that are technological, have been largely resolved. For example, Kane and Kay (1992) identified problems relating to timing synchronization between different types of hardware and various software applications. In a study of traditional and computerized neuropsychological assessment of mild brain injury, Bleiberg and associates (2000) listed 100 to 200 millisecond differences in response times on computer-based tasks as clinically significant; however, no mention of timing synchronization problems was mentioned. It should be noted that timing problems continue to exist with keyboard-based response mediums, although the WinSCAT avoids this problem by the exclusive use of the computer mouse for responses.

Other issues in the field of computerized neuropsychological assessment have gone largely unaddressed since the publication of the Kane and Kay (1992) review. These issues include: a lack of research on the construct validity of computerized tests (Kabat, et al., 2001); human factor limitations, including inadequate consideration of test instructions (Rohlman, Sizemore, Anger, & Kovera, 1996); and the relationships between traditional and computerized neuropsychological measures (Bleiberg et al., 2000). Given these issues, and the more general problem within clinical assessment of a lack of

understanding of the relationships between psychological tests (of any modality) and the theories that underlie them (Groth-Marnat, 2000), investigations that examine the relationships between traditional and computerized measures, with an emphasis on the cognitive constructs they measure, is indicated.

The Automated Neuropsychological Assessment Metrics (ANAM): Clinical Applications and Findings

Despite the advantages of computerized neuropsychological assessment methods over traditional neuropsychological assessment methods, broad-based implementation of this assessment modality has remained unrealized. One of the primary limitations with computerized neuropsychological assessment methods is the lack of empirical literature relating the existing computerized tests with existing traditional neuropsychological tests. Because of this lack of literature, the relationships between specific tests within the two testing methods (and how they relate to the broader cognitive domains they are posited to measure) has remained primarily conceptual and theoretical. The following literature search review summarizes those studies that have examined the Automated Neuropsychological Assessment Metrics (ANAM), a twelve-subtest battery of computerized measures designed to provide a mechanism for the assessment of cognitive functioning in repeated-measure administrations (Kane & Kay, 1992). This strategy was chosen because the five-test Windows version of the Spaceflight Cognitive Assessment Tool (WinSCAT) was created directly from tests among the larger ANAM battery.

A recent search in the scientific literature including the relevant terms for computerized neuropsychological assessment ("ANAM", "traditional", "neuropsychology") resulted in eight studies. All of the studies involved a clinical

population; no studies relating the ANAM with a medically and/or psychiatrically normal adult population was found. One study (Farmer, Cady, Bleiberg, & Reeves, 2000) measured cognitive efficiency of individuals during migraine attacks (N = 10) and after sumatriptan (a selective serotonin agonist targeting vascular receptors) injection (6 mg). The authors found a significant decrement in cognitive functioning during migraine, followed by recovery after sumatriptan injection. They also noted that this study was the first to document this pattern of findings (presumably based on the fine-grained analysis available with the ANAM performance assessment battery). Another study (N = 50) examined the utility of using computerized neuropsychological assessment of cognitive dysfunction in multiple sclerosis patients (Wilken, Kane, Sullivan, Wallin, & Usiskin, 2003). Moderate to high correlations (r = .40 to r = .69) between computerized and traditional neuropsychological measures in this clinical population were found, pointing to possible relationships between specific traditionally administered and ANAM tests.

Two studies (N = 117: Gottschalk, Bechtel, Maguire, Katz, Levinson, et al., 2002; and N = 28: Gottschalk, Bechtel, Maguire, Harrington, Levinson, et al., 2000) examined the relationship between traditional neuropsychological assessment tests with the ANAM measures (along with a computerized speech sample analyzer) in drug-abusing inpatients. In both cases statistically significant relationships between the tests (e.g., 2002 study highest r = .65; 2000 study highest r = .62) in the two administration modalities were found. Three studies looked at ANAM performance in subjects with mild brain injury or concussion. One of the studies (N = 122) (Bleiberg, et al., 2000), examining traditional neuropsychological tests and ANAM tests, found numerous significant correlations (r = .22 to r = .66) between them. Another study (N = 34) (Danial, Olesniewicz, Reeves,

Tam, Bleiberg, et al., 1999) found the ANAM to be sensitive to improvements in cognitive functioning in adolescents during a 4-month interval. The last of the three (N = 12) (Bleiberg, Garmoe, Halpern, Reeves, & Nadler, 1997) found that in a mild to moderate traumatic brain injury (TBI) population, performance on both traditional and computerized neuropsychological measures could be unimpaired initially but display abnormalities of sustained performance over subsequent days, punctuating the importance of sustainable, repeated-measure evaluation. A final study (N = 191) (Kabat, Kane, Jefferson, & DiPino, 2001) examined the relationship between traditional neuropsychological measures and the ANAM in an outpatient VA population with suspected neurocognitive dysfunction. Numerous statistically significant correlations (r = .17 to r = .66) between tests within the two modalities were found. This research furthers the growing literature on the relationship between traditional neuropsychological measures and the ANAM (the battery from which the WinSCAT was derived). However, the above findings from clinical samples do not provide information about WinSCAT performance or construct validity in a nonclinical, healthy, adult sample.

The Windows version of the Spaceflight Cognitive Assessment Tool (WinSCAT): Background

The WinSCAT is a series of computerized cognitive tests designed to assess aspects of a respondent's neurocognitive functioning. More specifically, it was designed by the NASA Integrated Product Team (IPT) (supported by work in several other locations including the Baltimore Veterans Medical Center, the San Diego Naval Medical Center, and the National Rehabilitation Hospital) to assist in assessing an astronaut's mental functioning while in space. Such factors as toxic exposures, sleep disruption,

illness, and excessive decompression are all risks that astronauts face. Given the high-risk nature of spaceflight, a system to monitor subtle changes in an astronaut's neurocoginitive performance was desired.

The NASA IPT identified a number of criteria that this new neurocognitive assessment tool had to meet in order to fulfill the identified requirements (Kane & Kay, 1997). These requirements for the assessment tool included:

1. It had to be comprised of tests capable of detecting changes in neurocognitive functioning resulting from a wide variety of factors (e.g., medical, environmental).
2. It had to be appropriate for repeated-measure use.
3. It had to take no longer than 15-20 minutes to administer.
4. It had to provide rapid performance feedback in an easily-understandable format.
5. It had to provide measures of not only accuracy but also response speed.
6. It had to be capable of updates based on future technological improvements.

Given the availability of nascent existing Department of Defense (DoD) neurocognitive assessment batteries (Kane & Kay, 1997), the NASA IPT decided to leverage existing technologies instead of developing a new product from the ground up. As the ANAM contained a format and tests that met the general requirements for the type of neurocognitive assessment tool being sought by the NASA IPT, ANAM was chosen as the superordinate system. With slight modifications to ensure the tests met the NASA IPT requirements listed above (e.g., number of test items shortened to reduce testing time), five ANAM tests were chosen and combined to produce the WinSCAT battery. The specific tests that were included in the battery were code substitution, running memory, mathematical processing, match-to-sample, and delayed code substitution

(memory) (Kane & Kay, 1997).

One advantage of the WinSCAT is that it is integrated as a routine part of a spaceflight crewmember's monthly medical check-up (i.e., periodic health status [PHS] test). This approach reduces the resistance to perform the task that might be encountered if it were perceived as a stand-alone, an extra, or a superfluous task (e.g., the MiniCog Rapid Assessment battery; Shephard & Kosslyn, 2005). Furthermore, the WinSCAT provides immediate feedback, in graphic or tabular format, of the testee's performance. It is designed and is used in a repeated manner, allowing for within-subject monitoring of performance over time. The WinSCAT was flight tested on the last Shuttle-Mir mission, and it is currently being used on the International Space Station (Kane et al., 1999; NASA Watch, 2005). It has also been used in the Mars Desert Research Station, a Mars-analog training base for future possible Mars missions (Osburg, Sipes, & Fiedler, 2003).

Despite ongoing use and plans for extensive future use, there is little published work in the empirical literature on the WinSCAT. Given that the WinSCAT consists of five ANAM subtests, the ANAM literature is representative of findings for the WinSCAT. However, given the sparse published literature that exists on the ANAM, and the fact that these published data represent findings in clinical populations, the need for more specific research on the WinSCAT is indicated.

Purpose and Specific Aims

The purpose of this doctoral dissertation research project was to examine the relationship between traditional neuropsychological tests and the WinSCAT computerized neuropsychological testing battery in a healthy, adult population. The

long-term goal of this project was to determine the appropriateness and applicability of computerized neuropsychological testing measures as compared with traditional neuropsychological assessment approaches for examining neurocognitive functioning in neurologically normal individuals. This project consisted of two studies (study 1, using existing data, and study 2, which involved new data collection) that will be presented separately.

Study 1: Existing (Archival) Data set

Specific Aim: Study 1 evaluated data that were previously collected from 99 healthy men and women to analyze and compare responses on computerized performance and traditional neuropsychological measures. (See Appendix A for a list of the traditional neuropsychological tests that were included in the collected data set.) The data set evaluated in study 1 was derived from two previously completed research protocols (see Appendix B through D) that included the traditional and computerized testing measures as part of larger project goals. The long-term goal of this aim is to determine the similarities and differences of selected computerized testing measures with a traditional neuropsychological screening battery designed to sample general intellectual ability, simple motor skills, and specific cognitive abilities across a broad array of cognitive domains in normal, healthy adults. Exploratory research in clinical adult samples comparing traditional neuropsychological tests with the computerized test battery has identified four cognitive domains of functioning from the traditional battery that also were evaluated by the computerized battery. These domains are: attention, executive functioning, memory, and visuospatial processing. Preliminary analyses (Retzlaff &

Vanderploeg, 1999) suggest that these four domains are similarly represented in the computerized battery with a healthy adult normal sample, but these findings have not been clearly established. Thus, study 1 specifically evaluated a nonclinical healthy adult sample to determine the relationships of a broad-based traditional neuropsychological test battery that evaluates eight cognitive domains of function (based on the conceptualization of the tests chosen for this archival study) with a computerized test battery that has been associated with four specific cognitive domains in clinical adult samples. The relationships between the traditional and computerized measures in a nonclinical healthy adult sample were evaluated with correlational and regression analyses.

Hypotheses and Rationale

The goal of study 1 in this doctoral dissertation research project was to evaluate the underlying cognitive construct structure of the WinSCAT computerized test battery using correlational and multiple regression analyses. Neuropsychological measures in a broad-based battery of traditional tests and the WinSCAT measures were compared in an archival data set. The purpose of this study was to examine the similarities of the interrelationships with previous WinSCAT findings in clinical populations.

The primary hypothesis of study 1 was that traditional and computerized measures that have been found to be significantly related to each other in clinical patient samples would be significantly related in healthy, adult samples. To evaluate this primary hypothesis, the interrelations among the traditional neuropsychological test measures were first evaluated to determine if the empirical relations among the traditional test measures reflected the specific theoretic cognitive domains they are purported to

represent (see Appendix E, Table 1.1, for proposed brain regions associated with these cognitive domains). These and all other correlations may be positive or negative, depending on the type of traditional task score (e.g., total correct versus total errors) and the specific WinSCAT metric (i.e., throughput) being compared. In all correlational analyses the expected direction for each pair of variables was known in advance of the analysis. Thus, a statistically significant direction in the non-predicted direction is not discussed as supportive for the hypotheses. Relations of the computerized tests with traditional tests that are believed to measure the same cognitive domains and with traditional tests that are not expected to measure the same domains were then examined to empirically determine the shared relations in healthy adults. In this study, this analysis was accomplished with an archival study comparing a broad-based traditional neuropsychological test battery with the computerized measures. The inclusion of the existing data set is beneficial by expanding the data available on the cognitive constructs evaluated by the WinSCAT, as well as by expanding the WinSCAT performance data set in a healthy, adult population. A list of the WinSCAT tests, and the cognitive domains associated with each test, is presented in Appendix E, Table 1.2.

HYPOTHESES

Hypothesis 1

Traditional neuropsychological measures that are putative measures of specific cognitive domains will demonstrate significant intercorrelations with each other within the specified domains. The direction of the correlation may be positive or negative depending on the type of measure (e.g., as performance for the tasks improves measures

involving completion time will be negatively correlated with measures involving raw number correct.)

A: The following measures of Attention will be significantly correlated– WAIS-III Digit Span maximum forward span, Symbol Search raw score, and Stroop Neuropsychological Screening Task (Stroop) Color subtest total completion time (in seconds).

B: The following measures of Executive Functioning will be significantly correlated - WAIS-III Digit Span maximum backward, Letter Number Sequencing raw score, COWAT total errors (FAS errors + Animal errors), Trail Making Test Part B raw time completion score, CVLT perseveration raw score, Wisconsin Card Sort Test failure to maintain set raw score, and Stroop Color-Word Task time to completion raw score.

C: The following measures of Verbal Memory will be significantly correlated - California Verbal Learning Test Short Delay Free Recall and Long Delay Free Recall raw scores, WMS-III Logical Memory (LM) 1st trial raw score, LMII raw score and LM percent retention raw score.

D: The following measures of Visuospatial Processing will be significantly correlated - WAIS-III Matrix Reasoning raw score, Rey-Osterrieth Complex Figure Test copy raw; WAIS-III Picture Completion raw score.

E: The following measures of Verbal Learning will be significantly correlated – CVLT-II slope raw score, CVLT-II total correct raw score, WMS-III LMI raw score.

F: The following measures of Visual Memory will be significantly correlated – ROCF delayed recall raw score, WMS-III Family Pictures I and II raw scores.

G: The following measures of Language Expression will be significantly correlated – Controlled Oral Word Association Test Letters (FAS) total correct and categories (Animals) total correct.

H: The following measures of Problem Solving/Reasoning will be significantly correlated – WAIS-III Similarities raw score, Shipley Abstract Reasoning raw score.

Rationale

Using a traditional neuropsychological paradigm, it is common to have many tests that measure different aspects of the same neuropsychological construct (Lezak, 1995). Studies utilizing both traditional and computerized neuropsychological measures have found significant correlations between traditional measures designed to measure similar cognitive domain constructs (Kabat et al., 2001). However, before examining the comparability of traditional and computerized measures in evaluating shared cognitive domain constructs, it is important to first demonstrate the empirical interrelationships among traditional neuropsychological measures as related to the respective, expected cognitive domains they are purported to measure. The neuropsychological battery that was developed for the two archival studies was designed to evaluate eight domains of neuropsychological functioning. Therefore, the interrelationships of the variables within each of those eight domains were examined in hypothesis 1.

Hypothesis 2

Traditional and computerized measures that have been found to evaluate the same cognitive domains in clinical samples will significantly correlate with each other in healthy nonclinical adult samples and will show weaker correlations between traditional and computerized measures on theoretically different domains.

A: Measures of Attention on the traditional battery (as described in Hypothesis 1 A above) will be significantly correlated with the WinSCAT code substitution learning task throughput score and will have weaker correlations with the throughput scores on the remaining WinSCAT tasks.

B: Measures of Executive Functioning on the traditional battery (as described in Hypothesis 1 B above) will be significantly correlated with the WinSCAT mathematical processing and running memory tasks throughput scores and will have weaker correlations with the throughput scores on the remaining WinSCAT tasks.

C: Measures of Memory on the traditional battery (as described in Hypothesis 1 C, E, and F above for the verbal memory, verbal learning and visual memory domains respectively) will be significantly correlated with the throughput score on the WinSCAT delayed code substitution task and will have weaker correlations with the remaining WinSCAT tasks throughput scores.

D: Measures of Visuospatial Processing on the traditional battery (as described in Hypothesis 1 D above) will be significantly correlated with the WinSCAT Match to Sample task throughput score and will have weaker correlations with the throughput scores on the remaining WinSCAT tasks.

E: Measures of Language expression on the traditional battery (as described in Hypothesis 1 G above) will be weakly correlated with the throughput scores on all five WinSCAT tasks.

F: Measures of Problem Solving/Reasoning on the traditional battery (as described in Hypothesis 1 H above) will be weakly correlated with the throughput scores on all five WinSCAT tasks.

Rationale

Previous research (Kabat et al., 2001; Bleiberg et al., 2000), utilizing regression analysis in clinical populations, demonstrated the predictive utility of computerized tests on traditional tests and cognitive domains. Ongoing research in normal populations (e.g., see Kane et al., 2005) indicates a similar pattern of findings. Of the eight discrete domains originally developed for use in the archival studies, three of the traditional neuropsychological battery domains were associated with one of the WinSCAT domains, and were thus collapsed together. Therefore, hypothesis 2 evaluated six traditional neuropsychological domains in relation to the four predicted WinSCAT domains.

Hypothesis 3

Computerized testing measures that evaluate specific cognitive domains will be found to significantly predict performance on composite measures of the respective cognitive domains in healthy adult samples. Because of the well-established relationship between general intellectual functioning and neuropsychological testing results, general intellectual functioning will be examined for inclusion as a covariate (Lezak, 1995).

Additionally, because the computerized metrics are sensitive to differences in motor functioning, the results of a motor task will also be examined as a potential covariate.

A: The throughput score on the WinSCAT code substitution task will predict a composite measure of Attention from the traditional battery (based on the measures described in Hypothesis 1 A above).

B: The throughput scores on the WinSCAT mathematical processing task and the running memory task will each predict a composite measure of Executive Functioning from the traditional battery (based on the measures described in Hypothesis 1 B above).

C: The throughput score on the WinSCAT delayed code substitution will predict a composite measure of Memory from the traditional battery (based on the measures of verbal memory, verbal learning and visual memory described in Hypothesis 1 C, E, and F above, respectively).

D: The throughput score on the WinSCAT match-to-sample task will predict a composite measure of Visuospatial Processing from the traditional battery (based on the measures described in Hypothesis 1 D above).

Rationale

Previous research utilizing factor analysis (Kabat et al., 2001; Bleiberg et al., 2000) in clinical populations has identified three WinSCAT factors. Visuospatial processing has been postulated as an additional independent factor (Kane et al., 2005.) Relationships between computerized measures and composite measures of the cognitive domains from traditional neuropsychological tests were expected to parallel the

relationships between computerized measures and the individual traditional neuropsychological test measures of the domain.

Research Design and Methods

The purpose of this doctoral dissertation research project was to examine the relationships between select traditional and computerized neuropsychological measures. Study 1 consisted of the analysis of previously collected data from two existing (archival) studies. Because the neuropsychological testing procedures were the same for the two archival studies and previous preliminary comparisons of the two studies indicated similar subject demographics, the data from both of these studies were combined. The WinSCAT analyses were based on the throughput score for each task (a measure of accuracy per unit of time). This score was chosen based on emergent data from newer studies of the WinSCAT indicating that the throughput scores are normally distributed, whereas the accuracy and response time measures (analyzed in previous studies) are not (Kane et al., 2005). The use of the throughput score is also consistent with recently published studies using some of the WinSCAT measures that showed decreases in performance efficiency following toxic exposure (Gamache, Levinson, Reeves, Bidyuk, & Brantley, 2005) and the effects of Alzheimer's disease (Levinson, Reeves, Watson, Harrison, 2004). Statistical analyses were completed with the Statistical Package for the Social Sciences software (SPSS for Windows, release 12.0.1).

Study Procedures

Overview: IRB approval was obtained for permission to analyze two existing data sets (1. "Randomized, Placebo-Controlled Study to assess the Safety of Combination Preventative Treatment with Pyridostigmine, DEET, and Permethrin" (active protocol) ("Pyridostigmine") and 2. "Tyrosine Effects on Physical and Cognitive Performance" (inactive protocol – open for data analysis only) ("L-Tyrosine"). Materials were submitted to the USUHS Graduate Education Office on 29 September 2003 for review and forwarding to the USUHS IRB (materials were received by the Office of Research on 9 October 2003). The dissertation author was involved in the collection of neuropsychological baseline test data that were collected prior to the start of the experimental portion in both studies. Data from the traditional and computerized measures that were collected in the baseline phases of both projects were combined and examined for outliers, missing data, and validity. The final total sample size was 99. EXCEL package software was used to create the spreadsheets for the traditional neuropsychological test battery data. The USUHS IRB approval letters, and the memoranda to the USUHS institutional review board by the principal investigators of the above studies permitting use of the data, are provided in Appendixes B and C.

Measures

Demographic Information: To evaluate the potentially confounding contributions of demographic variables to relationships between the traditional and computerized testing measures in the existing data set, the relationships of subjects' age, gender, ethnicity, and education with the predictor WinSCAT measures were evaluated. If

significant relationships of demographic variables were obtained with any of the predictor measures, then the demographic variable(s) were included in the hypothesis 3 analyses for evaluation in the regression analysis.

Traditional neuropsychological measures: The measures that were evaluated in this study are based on a 2-hour neuropsychological screening battery that encompassed general intellectual functioning and simple motor skills, as well as the eight cognitive domains of attention, verbal learning, verbal memory, visual memory, visuospatial abilities, language, problem solving/reasoning, and executive functioning skills. All of the measures used are well-validated, reliable, and standardized, with good psychometric support for their use in evaluating these cognitive domains (Lezak, 1995; Groth-Marnat, 2000). Additionally, both the Pyridostigmine and L-Tyrosine studies utilized the same neuropsychological screening battery. The specific measures that were used in these batteries included: the Shipley Institute of Living Scale, the Grooved Pegboard Test, the California Verbal Learning Test, the Rey-Osterrieth Complex Figure Test, the Trail Making Test, Parts A and B, the Stroop Color-Word Interference Test, the Controlled Oral Word Association Test (COWAT), two Wechsler Memory Scale III (WMS-III) subtests (Logical Memory and Family Pictures), and seven Wechsler Adult Intelligence Scale – III (WAIS-III) subtests (Picture Completion, Information, Similarities, Matrix Reasoning, Symbol Search, Letter-Number Sequencing, and Digit Span). A list of these tests and their respective administration times are provided in Appendix A. The cognitive domains represented by each test for examination in hypotheses 1, 2 and 3 are presented in Appendix E, Tables 1.3a-c. All identification data for this study were coded. No connection between the subject's actual identification and the study

identification code was available in these data. The scoring for these tests normally involves obtaining a raw score, and then converting that raw score into a standard score. In this study, raw scores (or other direct measures, e.g., number of errors) were used in the analyses. This technique attenuates the possible restriction of range effects that results from standardizing the test results (e.g., using an age-adjusted standard score) in a fairly homogeneous population.

Computerized neuropsychological measures: The WinSCAT is a series of five computerized neuropsychological measures associated with a number of neurocognitive constructs including reaction time, attention and concentration/working memory, learning and memory, spatial perception, and speeded arithmetic calculation abilities. The specific WinSCAT tests are code substitution, running memory, mathematical processing, match-to-sample, and delayed code substitution. The WinSCAT measures have a total of ten scores but only the throughput score (a measure of accuracy per unit of time) is of direct interest for the present study. The WinSCAT was the computerized neuropsychological metric used in both the Pyridostigmine and L-Tyrosine studies. The WinSCAT data administration, necessary format conversions, etc., were carried out in conjunction with procedures developed by Robert Kane, Ph.D., principal contractor for the development of the WinSCAT database.

Subjects description: The subjects for both the Pyridostigmine and L-Tyrosine studies were 99 healthy, moderately to highly physically fit adults. The majority of the sample were Caucasian males with at least a college degree (see Table 1). An unstamped copy of the informed consent document, which provides a brief summary of the purpose, experimental goals, and exclusion criteria for participation in the Pyridostigmine project,

the official informed consent approval, and permission by the principal investigator to use the data, are provided in Appendix B. A summary of the goals and purposes of the L-Tyrosine study, the exclusion criteria, the informed consent approval, and permission by the principal investigator to use the data, are provided in Appendix C.

Procedures: The procedures for the Pyridostigmine study are included in Appendix B, sections 2 and 3. The procedures for the L-Tyrosine study are included in Appendix C. Subjects for both the Pyridostigmine and L-Tyrosine studies were recruited through advertisements in the local media, on the Internet, and through use of flyers on the USUHS campus. The informed consent documents for the Pyridostigmine and L-Tyrosine studies are included in Appendices B and C, respectively. The L-Tyrosine study was conducted from 2000 to 2002, and the Pyridostigmine study commenced in 2001 and is ongoing (for data analysis only). The health status of the subjects in both studies was established by a telephone interview to screen out specific factors (age, body weight, use of medications, psychiatric history, etc.) that, in association with those studies' specific aims, could impact the experimental outcomes. Potential subjects then reported to a laboratory (the Human Performance Laboratory [HPL] at USUHS) for a screening evaluation to determine study eligibility. A staff physician and/or research nurse obtained informed consent from subjects at this point. A board certified physician conducted a medical history and examination to assess whether subjects appeared to be in a sufficient state of health to participate in the (respective) study. Subjects who qualified for inclusion in the study were then scheduled for completion of the pre-experimental baseline data collection and for the subsequent experimental portions. During the baseline data collection phase, each subject completed six trials of the WinSCAT battery,

several measures of physical performance, a packet of psychometric questionnaires relevant to the respective study's experimental design, and a two-hour neuropsychological screening evaluation designed to evaluate performance across a broad array of cognitive domains.

On day 1 of each respective (Pyridostigmine and L-Tyrosine) study, the subject reported back to the HPL (in the morning, typically from 0700-0800 hours) for completion of the initial baseline assessment procedures. At this time, the first trial of the WinSCAT battery was administered and additional baseline measures were taken. In both the Pyridostigmine and L-Tyrosine studies, the initial trial for the WinSCAT was supervised. After completion of the WinSCAT, the subject was escorted by one of the three neuropsychological test examiners to the Neurocognitive Laboratory, located in a separate small room adjacent to the cafeteria on the USUHS campus. At this time, demographic information was collected. These data included: the date of testing, age, gender, ethnicity/race, education, preferred handedness for writing, medication use, previous experience with neuropsychological testing, and the identification of the researcher conducting each examination. The neuropsychological screening battery was then administered (see Appendix A). In both studies, all baseline data on the traditional neuropsychological battery were collected in the morning between the hours of 0730 and 1100. Administration of the traditional neuropsychological tests was completed with standardized instructions that were provided in the Neurocognitive Laboratory. Standardization of instructions for each task was maintained by the required use of a 5-inch by 7-inch spiral card set that remained on the test table on a small flip-chart easel. The test battery was consistently administered in the same specific order with each

subject. In both studies, all baseline data were collected before the commencing of the experimental manipulation phases. Therefore, the baseline phase data from the traditional and computerized neuropsychological tests that were evaluated in study 1 of this research project were in no way impacted by the experimental manipulations of the archival studies.

Risks/Benefits

There were no foreseen risks for participation in the neuropsychological testing component of the study, and no adverse events occurred. The testing component of the overall procedure was short (approximately 2 hours) and the participants were compensated based on their completion of the particular study (i.e., Pyridostigmine and L-Tyrosine) in which they were participating. All subjects were thanked for their participation in the testing procedure and it was explained to them that their participation would contribute to the empirical literature.

Data Analyses

This study employed bivariate correlations and multiple regression analyses involving bivariate correlations and forced-entry regression equations to test the hypotheses. Bivariate correlations were used in the primary analyses to examine: 1) the relationships among the traditional neuropsychological measures that purportedly evaluate the same cognitive domains, and 2) the relationships between composite measures of those traditional domains with the WinSCAT tasks that have been found to represent those domains in clinical patient samples. Multiple regression is a general

technique that is used in order to test the strength of relationships between multiple predictors and a single outcome measure (Cohen & Cohen, 1983), and is consistent with the existing analytic methodology employed in the scientific literature for evaluating the relationships between traditional neuropsychological measures and the computerized tests contained in the WinSCAT battery (e.g., Kabat et al., 2001; Bleiberg et al., 2000; Wilken et al., 2003). Given the ongoing efforts to establish the neurocognitive constructs tapped by the WinSCAT tests (e.g., Retzlaf & Vanderploeg, 1999) the examination of the extent to which the WinSCAT measures predict performance on traditional neuropsychological tests (and the well-established cognitive domains they measure) is warranted. All statistical analyses were completed with the Statistical Package for the Social Sciences software (SPSS for Windows, release 12.0.1).

It should be noted that the WinSCAT measure of interest in all present study analyses is the throughput score for each task. Other studies with the WinSCAT using a regression model (e.g., Kabat et al., 2001) have used an analytical procedure to decide which WinSCAT measure (speed, accuracy, or throughput) to use. In those studies, instead of using the throughput score exclusively, the one metric from each WinSCAT measure that had the highest correlation with the dependant measure was entered into the regression. This departure in analytic technique in the present study is based on the ongoing research demonstrating the lack of normality of distribution of the reaction time and accuracy measures, making their specific use as measures less desirable. In contrast, the throughput measure (which combines speed and accuracy) shows good normality of distribution as well as good stability (Kane et al., 2005). Missing data for the traditional

neuropsychological data were handled with the pairwise deletion method, and with the listwise method for the WinSCAT data.

In order to test the overarching and sub-components of hypothesis 1, simple bivariate correlations for all the traditional neuropsychological tests were calculated. For hypothesis 2, simple bivariate correlations were calculated for all the traditional neuropsychological tests (organized by cognitive domains) compared with all of the computerized measures. Three sets of memory measures were combined, resulting in a change of the number of hypotheses (from eight to six). The bivariate correlation matrix was calculated independently (i.e., without covarying potential confounds) in order to evaluate the hypotheses.

For hypothesis 3 the relationships of subject demographics, general intellectual functioning and dominant hand motor performance (all potential confounds) with the WinSCAT test measures were first evaluated using bivariate correlations, independent samples t-tests or between-groups ANOVA analyses as appropriate for the distribution of the potential confound variable. The outcome measures (dependant variables) for the multiple regression analyses in hypothesis 3 were composite cognitive domain scores that were derived from the relevant individual traditional neuropsychological testing measures. Two domain scores that were not expected to be related to the WinSCAT measures were eliminated, resulting in the four cognitive domains of analysis (attention, executive functioning, memory, and visuospatial processing). The primary predictor variables were the respective WinSCAT measures that are believed to represent the same cognitive domains as the traditional composite measures. The regression analyses used two-tailed tests, and the alpha level was set at $p<0.05$.

To create the outcome measures to be predicted by the WinSCAT measures in hypothesis 3, the traditional neuropsychological measures that evaluate each specific cognitive domain were combined into a composite summary domain score that was an average of the contributing measures' standardized z scores (with each test being equally weighted). Standardized z scores for the contributing measures were created by subtracting each respective measure's mean score from each subject's raw score on that measure before dividing that difference score by the respective measure's standard deviation. This process resulted in 4 composite cognitive domain z scores, one each for attention, executive functioning, memory, and visuospatial processing. The tests included in each domain for hypothesis 3 in this study are shown in Appendix E, Tables 1.3c.

The regression models that were evaluated for hypothesis 3 first entered (as a block) those demographic variables that were significantly associated with any of the predictor WinSCAT measures with either statistical significance (t-test and ANOVA comparisons) or at $r = .3$ or higher (Pearson correlation analyses). These criteria were selected based on relationships found between demographic variables and the relationship between traditional neuropsychological tests and WinSCAT tests in the existing literature (e.g., Bleiberg et al., 2000). The measure of estimated general intellectual functioning was then entered as the second step in the regression equation if it was shown to be significantly related to any of the WinSCAT measures in bivariate correlation analyses. This same procedure was applied to examine the potential inclusion of the measure of simple motor skills. The last step in the regression analysis was to enter the WinSCAT

throughput measure of interest. In all regression analyses, the relevant cognitive domain z score was the dependant variable to be predicted from the model.

Power and Sample Size

The sample size calculations for this study were selected by using the findings of previous research (Bleiberg et al., 2000; Kabat et al., 2001) on this topic. In their clinical populations, they found statistically significant relationships between the traditional neuropsychological tests and the WinSCAT tests at the r = .20 to r = .30 level(s). In this study of normal subjects, a level of r = .40 is postulated as a conservative estimate of the expected magnitude of the correlation required to reach statistical significance. Given that assumption and an alpha level of .05, the estimated sample size needed for this study is 79 (NQuery Advisor Analysis Software). This sample size is consistent with the empirical literature examining the relationship between traditional and computerized neuropsychological measures (previously reviewed in the ANAM section), whose average sample size was 71.

Study 1 Results

Summary of Results Presentation

The primary hypothesis for this study was that traditional and computerized neuropsychological measures that have been found to be significantly related to each other in clinical patient samples would be significantly related in a healthy adult sample. Three different primary hypotheses were proposed, and each primary hypothesis was further broken down by the specific tests and/or cognitive domain(s) being analyzed. In

this study, the number of sub-hypotheses was eight for hypothesis 1, six for hypothesis 2, and four for hypothesis 3.

The results are presented in the order of the hypotheses. Before hypothesis 3 is reported, the relationships of the demographic information with the primary predictor variables (WinSCAT throughput scores) are reported, for use as covariates in the analyses as appropriate when related to the predictors.

Hypothesis 1

Traditional neuropsychological measures that are putative measures of specific cognitive domains will demonstrate significant intercorrelations with each other within the specified domains. The direction of the correlation may be positive or negative depending on the specific measures being analyzed, but the expected direction was known a priori based on the purported relations among those variables measuring similar domains. As a result, all correlations were evaluated with one-tailed significance levels set at $p<.05$.

The final sample size on which valid data on the traditional neuropsychological test battery were available for analyses in hypothesis 1 (H1) was N=99. H1 was broken down into a total of eight sub-hypotheses (A-H), one for each cognitive domain. The cognitive domains that were evaluated with the traditional neuropsychological measures were attention (three measures), executive functioning (seven measures), verbal memory (five measures), visuospatial processing (three measures), verbal learning (three measures), visual memory (three measures), language expression (two measures), and problem-solving/reasoning (two measures.) Of the total 45 intercorrelations that resulted from the eight within-domain analyses, 33 (73%) were statistically significant ($r \geq \pm.18$).

Of the 33 statistically significant correlations, 11 were of a small magnitude ($r \geq .10$ to $r < .30$), 17 were of a moderate magnitude ($r \geq .30$ to $r < .50$), and 5 were of a large magnitude ($r \geq .50$) (Cohen, 1988). On six of the eight domains (attention, verbal memory, visuospatial processing, visual memory, language expression, and problem-solving/reasoning), all tests within the domain were significantly intercorrelated with each other ($p < .05$) (see Tables 2-9).

On the attention domain (H1:A, Table 2) the hypothesis was strongly supported, as all measures were significantly intercorrelated with at least a moderate magnitude of the strength of the relationships ($p < .05$, $r \geq \pm .32$). On the executive functioning domain (H1:B, Table 3) the hypothesis was partially supported; of the seven executive functioning measures, only one measure (Wisconsin Card Sort Test failure to maintain set total raw score) was not correlated with any of the other executive functioning measures. The remaining six measures were significantly correlated with at least one other measure within the domain ($p < .05$, $r \geq \pm .19$ to .57). On the verbal memory domain (H1:C, Table 4) the hypothesis was supported and all measures were significantly intercorrelated ($p < .05$, $r \geq \pm .18$). On the visuospatial processing domain (H1:D, Table 5) the hypothesis was fully supported and all measures were significantly intercorrelated ($p < .05$, $r \geq \pm .27$). On the verbal learning domain (H1:E, Table 6) the hypothesis was supported and each of the three measures were significantly correlated with at least one other measure in that domain ($p < .05$, $r \geq \pm .20$). On the visual memory domain (H1:F, Table 7) the hypothesis was strongly supported and all measures were significantly intercorrelated with at least a moderate magnitude of the strength of the relationships ($p < .05$, $r \geq \pm .45$). On the language expression domain (H1:G, Table 8) the hypothesis

was strongly supported and the measures were significantly intercorrelated with at least a moderate magnitude of the strength of the relationships ($p<.05$, $r = .47$). On the problem-solving domain (H1:H, Table 9) the hypothesis was strongly supported and the measures were significantly intercorrelated with at least a moderate magnitude of the strength of the relationships ($p<.05$, $r = .37$).

Hypothesis 2

Traditional and computerized measures that have been found to evaluate the same cognitive domains in clinical samples will significantly correlate with each other in a healthy nonclinical adult sample and will show weaker correlations between traditional and computerized measures on theoretically different domains. The direction of the correlation may be positive or negative depending on the specific measures being analyzed, but the expected direction was known a priori based on the purported relations among those variables measuring similar domains. As a result, all correlations were evaluated with one-tailed significance levels set at $p<.05$.

Validity of the scores obtained on the traditional neuropsychological and WinSCAT measures was evaluated based on ranges (e.g., no accuracy percentages above 100 or below 60 if based on a dichotomous variable) and analyses were conducted using only subjects determined to have valid results. To ensure maximal data quality, if an invalid metric for a subject on any WinSCAT measure was found, that subject was excluded from further analyses for all WinSCAT measures. Invalid data on neuropsychological measures precluded use of that subject for the analyses involving the specific measure. WinSCAT throughput measures were found to be similar to other

studies of WinSCAT performance (e.g., Bleiberg, Cernich, Cameron, Sun, & Peck, 2004). The final sample size on which valid data were available on both the traditional neuropsychological test battery and all of the computerized measures for analyses in hypothesis 2 (H2) was N=64. H2 was evaluated with a total of six sub-hypotheses; one for each of the cognitive domains that had been found to be related in clinical patient samples (tests from three of the domains evaluated in H1 were collapsed into a single memory domain in H2 so as to be more directly comparable to the analyses with clinical samples reported in the literature, on which this primary hypothesis was based). The cognitive domains that were evaluated from the traditional neuropsychological measures were attention (three measures), executive functioning (seven measures), memory (eleven measures), visuospatial processing (three measures), language expression (two measures), and problem-solving (two measures.)

Of the total 31 intercorrelations that resulted from the expected relations between each traditional neuropsychological domain and the computerized measure hypothesized to represent the same domain, 20 (65%) were statistically significant at $p<.05$ ($r \geq \pm.23$). Of the 20 statistically significant correlations, 3 were of a small magnitude ($r \geq .10$ to $r <.30$), 15 were of a moderate magnitude ($r \geq .30$ to $r <.50$), and 2 were of a large magnitude ($r \geq .50$) (Cohen, 1988). On one of the four expected domains to have relationships with one or more of the computerized measures, all tests within that domain (i.e., attention) were significantly correlated with the expected computerized measure (computerized code substitution learning; 'CDLTP') ($p<.05$); see Table 10.

Of the total 89 intercorrelations between the four traditional neuropsychological domain measures (attention, executive functioning, memory, visuospatial processing) and

the specific computerized measures that were not expected to be related, 35 (39%) were statistically significant at $p<.05$ ($r \geq \pm.21$). Of the 35 statistically significant correlations, 15 were of a small magnitude ($r \geq .10$ to $r <.30$), 19 were of a moderate magnitude moderate ($r \geq .30$ to $r <.50$), and 1 was of a large magnitude ($r \geq .50$) (Cohen, 1988). Lastly, of the 20 intercorrelations between the two traditional neuropsychological domain measures (language expression, problem solving) and the computerized measures that were not expected to be related, 6 (30%) were statistically significant at $p<.05$ ($r \geq \pm.22$). Of these, 2 were of a small magnitude ($r \geq .10$ to $r <.30$) and 4 were of a moderate magnitude ($r \geq .30$ to $r <.50$) (Cohen, 1988); see Table 10. Overall, of a total of 140 intercorrelations, significant correlations ($p<.05$) were found between the traditional neuropsychological measures and the computerized measures on 61 measures across all six of the domains (see Table 10).

Hypothesis 3

Computerized testing measures that evaluate specific cognitive domains will be found to significantly predict performance on composite measures of the respective cognitive domains from the traditional neuropsychological measures in healthy adult samples. Because of the well-established relationship of demographic variables and general intellectual functioning with neuropsychological testing results, these variables were examined for potential inclusion as covariates (Lezak, 1995). Additionally, because the computerized metrics are sensitive to differences in motor functioning, dominant hand performance on a speeded motor dexterity task was examined as a potential covariate.

Potential contributions of demographics, estimated intellectual functioning, and dominant hand motor dexterity speed scores to the predictor WinSCAT throughput scores were evaluated with bivariate correlations (age, education, estimated intellectual functioning, and motor speed), independent samples t-tests (gender), or analysis of variance (ethnicity). Based on several statistically significant findings between demographic factors, general intellectual functioning, and the motor task with performance on the computerized tasks, several of these factors were included as control variables in the regression analysis. Education level and estimated intellectual functioning were found to be significantly correlated ($p<.05$) with three of the five WinSCAT measures (education with code substitution learning throughput [CDLTP], running memory throughput [RMTP], and mathematical processing throughput [MTHTP]; estimated intellectual functioning with code substitution learning throughput [CDLTP], mathematical processing throughput [MTHTP], and code substitution delayed throughput [CDDTP]). Age, gender, and motor speed (but not ethnicities) were each found to have at least one significant relationship with one of the WinSCAT tasks (see Tables 11a – 11e).

The final sample size on which valid data were available for the regression analyses to evaluate hypothesis 3 (H3) varied between 57 and 89. This variation was due to differences between valid data on specific tests that comprised the combined domain score for the cognitive constructs in question. There were a total of four sub-hypotheses, one for each of the four final cognitive domains (the tests from two domains that were not predicted to be related to the existing domains [based on the clinical literature] were eliminated from H2, resulting in the change from six cognitive domains to four.) One of

the cognitive domains, executive functioning, was hypothesized to have two different computerized measures as significant predictors. The predicted cognitive domain composite scores from the traditional neuropsychological measures were attention, executive functioning, memory, and visuospatial processing. The final analyses consisted of a four-block regression analysis for each predictor, with significant demographic variables entered in the first block, general intellectual functioning in the second block, motor task performance in the third block, and the computerized test (the predictor of interest) in the fourth block. Results from the five analyses associated with the five WinSCAT predictor measures are shown in Tables 12 – 16.

On the attention domain (H3:A, Table 12), the hypothesis was supported. The results of the four-block hierarchical regression indicated that the overall model was significant (adjusted $R^2 = 0.34$, $p<.05$). In addition, the amount of additional variance accounted for by the code substitution learning task was statistically significant and of a moderate magnitude in predicting Attention test performance after the control variables were accounted for (R^2 change = 0.09, $p<.05$). On the executive functioning domain (H3:B, Tables 13 and 14), the hypothesis was supported for one WinSCAT task and was not supported for the other WinSCAT task. The results of the four-block hierarchical regression indicated that the overall models were significant for both analyses. On the mathematical processing task (Table 13), the overall model was statistically significant (adjusted $R^2 = 0.21$, $p<.05$) but the mathematical processing task did not predict an independent amount of the variance on Executive Functioning test performance after the other control variables were accounted for (R^2 change = 0.05, $p>.05$). On the running memory task (Table 14), the overall model was significant (adjusted $R^2 = 0.26$, $p<.05$)

and the running memory task was statistically significant and of a moderate magnitude in predicting a significant amount of the variance on Executive Functioning test performance after accounting for the control variables (R^2 change = 0.09, $p<.05$). On the memory domain (H3:C, Table 15), the hypothesis was supported. The results of the four-block hierarchical regression indicated that the overall model was significant (adjusted R^2 = 0.40, $p<.05$). In addition, the code substitution delayed memory task was statistically significant and of a small magnitude in predicting a significant amount of the variance on Memory test performance after the control variables were accounted for (R^2 change = 0.07, $p=.05$). On the visuospatial processing domain (H3:D, Table 16), the hypothesis was not supported. The results of the four-block hierarchical regression indicated that the overall model was significant (adjusted R^2 = 0.39, $p<.05$). However, the match-to-sample task did not predict a significant amount of the variance on Visuospatial processing test performance after the control variables were accounted for (R^2 change = 0.01, $p>.05$).

Discussion

Based on the results of study 1, in a healthy adult sample, significant relationships were found to exist between traditional and computerized neuropsychological measures that purport to test performance in similar cognitive domains. Even when controlling for many demographic variables (i.e., age, gender, and education) that could potentially impact WinSCAT performance, many of these relationships remained. The findings on this archival data set provide partial support for all three primary hypotheses.

In hypothesis one, the traditional neuropsychological measures commonly believed to represent specific cognitive domains were generally found to do so. The executive functioning domain included measures from two traditional neuropsychological tests (WCST failure to maintain set and COWAT total errors) that did not correlate strongly with the other executive functioning test measures. However, failure to find highly significant intercorrelations of these two measures with the other measures in this domain is not surprising. In both cases, the measures of interest were both error scores, and few errors were committed. In these two tests, the existence of these errors is widely evaluated in a dichotomous fashion, with the existence of even a few errors often characterized as a pathognomonic sign of frontal lobe dysfunction (Lezak, 1995). In this high functioning, non-clinical, and highly educated population, the restriction of range of these measures, due to the few number of errors that occurred, is not surprising.

In hypothesis two, the selected traditional neuropsychological tests that represented the cognitive constructs of interest were generally found to correlate with the WinSCAT measure of the same cognitive domain, and to correlate less with other domains (see Table 10). However, there were some exceptions to this finding. For example, the tests comprising the attention domain (Digit Span, Symbol Search, and Stroop Neuropsychological Screening Test) not only significantly correlated with the WinSCAT attention measure (code substitution learning) but also with one of the WinSCAT executive functioning measures (running memory). In fact, of the fifteen total correlations of these three traditional attention domain measures with the five WinSCAT measures, ten were statistically significant (three of the five not significant findings involved the WinSCAT memory domain measure.) One interpretation of these findings

is that these traditional tests tap a diffuse general attention function that does not represent a specific cognitive domain but rather a moderating neurocognitive function. Obviously, without adequate functioning on tasks associated with attention, performance on any focused test would be expected to be adversely impacted. Therefore, it is not surprising that these tests were significantly associated with four of the five WinSCAT measures across three different domains represented by the computerized tasks.

In hypothesis three, the WinSCAT measures that were predicted to significantly relate to performance on the respective traditional measures represented in composite domain scores were found to do so for three of the four predicted domains, although only three of five independent analyses were significant. Specifically, the two WinSCAT tasks of math processing and running memory were independently hypothesized to predict the traditional executive functioning cognitive domain score, but a significant result was only obtained for running memory (see Table 14) with a trend for significance with the WinSCAT math processing task ($p = .08$) (see Table 13). The prediction regarding the traditional composite score for the visuospatial cognitive domain was the only fully unsupported finding in hypothesis three, wherein the WinSCAT match-to-sample task was not a significant predictor of visuospatial processing. Based on the regression model for the visuospatial processing construct, 36% of the variance was accounted for by the measure of general intellectual functioning with no notable additional variance accounted for by the WinSCAT measure (see Table 16).

One explanation for this null finding is suggested by non-significant intercorrelations of the WinSCAT match-to-sample task with the individual traditional neuropsychological measures expected to be related to and stronger correlations with

other traditional measures as evidenced in Table 10. Based on the significant correlations that were identified, the WinSCAT match-to-sample task may have particularly multifaceted performance requirements, involving attention, executive functioning, and memory processes that overshadow any contributions from visuospatial processes per se. This idea is consistent with the findings in one prior study of the factor structure of the WinSCAT tests, in which it was found that the accuracy measure of the match-to-sample test provided unique variance to the overall factor structure of the WinSCAT (Bleiberg et al., 2000).

When considering the above issues, these generally positive findings for the WinSCAT measures in study 1 are particularly significant in light of the fact that several classes of variables that were significantly correlated with WinSCAT test performance were accounted for before considering the independent predictive value of the WinSCAT measure in question.

The findings from this study differ in some ways from the previous research in this area (e.g., Bleiberg, Kane, Reeves, Garmoe, & Halpern, 2000; Kabat et al., 2001; Retzlaff & Vanderploeg, 1999). In general, most of the relationships between the traditional neuropsychological tests and the WinSCAT tests were of a lesser magnitude in the present study. For example, in this study, only three of one-hundred forty correlations (2%) between all of the traditional measures and the WinSCAT measures were greater than $r = 0.5$ (see Table 10). In the Bleiberg et al. (2000) study, three of the forty-three correlations (7%) presented were equal to or greater than 0.5 (Bleiberg et al., 2000). In the Kabat et al. (2001) study, twelve of the thirty-two correlations (38%) presented were greater than $r = 0.6$ (Kabat et al., 2001). Interestingly, significant

differences in the relationships between education and test performance were found in the present study when compared to prior studies. For example, in the Kabat et al. (2001) study, the correlation between education and WinSCAT performance was r = .13. In this study, the correlation between education and WinSCAT performance was r = .38.

Several reasons for these between-study differences are possible. The subject populations for this study differ significantly from previous studies on this topic in that this study was limited to an evaluation of healthy adults. Previous studies utilized purely clinical populations (e.g., with known or suspected neurocognitive deficits; Kabat et al., 2001) or populations that included subjects with conditions known to impact cognitive test performance (e.g., ADHD; Bleiberg et al., 2000). This factor could account for the discrepancy in the relationship between education and WinSCAT performance noted above, in that the sequelae of the clinical condition could itself create a performance-limiting factor that a nonclinical population would not be subject to.

Another important factor that impacts comparison of this study with previous related studies is test selection and test administration factors. Test selection for the traditional measures in the two studies that were combined for study 1 varied from measures evaluated in clinical studies. While some of the tests are the same, many are not. However, even in cases where the same tests were used between the present study and previously published studies with clinical samples, other more general test administration factors such as test battery length, test intensity (e.g., timed tests), perceived difficulty, and order of administration, may have created differential diffuse effects on overall neuropsychological test performance between studies.

Lastly, the data analytic methodology differed for this study compared to previous studies in several ways. In this study, numerous potential confounding variables (demographic, intellectual, and motor skills) were accounted for in the final regression analysis. The removal of these factors from the analysis would undoubtedly change the relative predictive value of the WinSCAT measure to the cognitive construct in question. Also, in this study, the WinSCAT analysis was limited to throughput scores only (a measure of accuracy per unit of time). This was based on emergent data from newer studies of the WinSCAT indicating that the throughput scores are normally distributed, where as accuracy and response time measures (analyzed in previous studies) are not (Kane et al., 2005).

Limitations

Several limitations of this study are noteworthy. The subjects were a fairly homogeneous group in that they were healthy normals, young, mostly male and Caucasian, and highly educated (see Table 1). Additionally the comprehensive screening procedures, demanding physical requirements, and extensive time commitment required of the two studies that comprise study 1 (see Appendixes B and C), resulted in a subject population that cannot be expected to provide a representative sample of the general nonclinical population as a whole.

The traditional neuropsychological measures evaluated in this study were determined on the basis of available samples from two existing data sets. The tests that had been included in the original studies were chosen by an experienced clinical neuropsychologist and, based on the extensive literature of neuropsychological tests, are

valid measures of the domains in which they were combined to represent for the present study. However, the purposes for which the measures were originally selected were not specifically based on their potential relationship to the tests of the WinSCAT (W. A. Law, personal communication, 12 July, 2005).

The data analytic technique in the regression portion of this study was designed to control for possible contributing variables that might otherwise explain any significant predictions between the WinSCAT and traditional cognitive domains. The specific variables included education and intellectual functioning. However, given the fairly high education, and high and restricted range of intellectual functioning in this population (estimated total full-scale intelligence of 112.8, SD = 7.2), this technique may have reduced variance without correspondingly increasing the meaningfulness of the data.

The test administration procedures for the WinSCAT in the two independent research projects that comprise the data in study 1 were such that they were both supervised but non-standardized. Therefore, likely procedural differences in test administration occurred. While this flexibility can be a benefit of computerized neuropsychological assessment batteries in a clinical context, in the research arena it may be problematic in that it may have introduced variation in the subjects' understanding of the task requirements and, subsequently, in their task performance. Furthermore, the presence or lack of another individual for monitoring in the WinSCAT testing context could have impacted the subject's performance via changes in situational anxiety (e.g., induction of higher anxiety due to performance concerns; reduction of performance anxiety with the reassurance of an examiner's presence, etc). The impact of this factor was most likely minimized by the utilization of data selection criteria for the WinSCAT

tests (e.g., a minimum accuracy score) to determine whether the results to be included in the analyses were valid. However, the non-standardized approach in administration across the two existing studies from which these data were derived undoubtedly introduced additional variance in the WinSCAT results.

In summary, despite the benefits of this study, it had several weaknesses. These included the nature of the subject population (e.g., young and very physically fit), the lack of traditional neuropsychological tests chosen specifically for their expected relationship to WinSCAT measures, and the procedural differences that existed between the two studies that were combined for this study. In order to address these weaknesses, new data collection was also completed, with a different subject population, traditional neuropsychological tests chosen a priori, and standardized test administration procedures. It was believed that these limitations could be minimized by new data collection with a broader, more diverse population, with traditional neuropsychological tests chosen for their applicability to the WinSCAT measures, and with standardized test administration procedures. These factors were taken into account in the creation and execution of study 2. Additionally, the inclusion of both the archival as well as the prospectively-collected data set were expected to be more beneficial then either would be alone by expanding the data available on the cognitive constructs evaluated by the WinSCAT, as well as by expanding the WinSCAT performance data set in a healthy, adult population.

Study 2: Prospectively-Collected Data set

Specific Aim: Study 2 measured and compared responses of a sample of 75 nonclinical adult men and women (different from the participants in study 1) on a narrowly-focused

traditional neuropsychological test battery that was designed to specifically evaluate performance on the four cognitive domains (i.e., attention, executive functioning, memory, and visuospatial processing) that have been empirically derived from the computerized neuropsychological test battery in the published literature. Thus, study 2 was designed to determine if the cognitive domains that have been found to be shared between the computerized battery and traditional tests in clinical samples can be generalized to a healthy, nonclinical, adult sample.

Hypotheses and Rationale

The overarching goal of this doctoral research project was to evaluate the underlying cognitive construct structure of the WinSCAT computerized test battery using correlational and multiple regression analyses. The neuropsychological constructs of attention, executive functioning, memory, and visuospatial processing were specifically examined in both traditional and computerized measures and were compared across the traditional and computerized batteries in a prospectively-collected data set.

The primary hypothesis of this project was that traditional and computerized measures that have been found to be significantly related to each other in clinical patient samples would be significantly related in healthy, adult samples. To evaluate this primary hypothesis, the interrelations among the traditional neuropsychological test measures were first evaluated to determine if the empirical relations among the traditional test measures reflected the specific theoretic cognitive domains they are purported to represent. These and all other correlations may be positive or negative, depending on the type of traditional task score (e.g., total correct versus total errors) and the specific

WinSCAT metric (i.e., throughput) being compared. In all correlational analyses the expected direction for each pair of variables was known in advance of the analysis. Thus, a statistically significant direction in the non-predicted direction is not discussed as supportive for the hypotheses. Relations of the computerized tests with traditional tests that are believed to measure the same cognitive domains and with traditional tests that are not expected to measure the same domains were then examined to empirically determine the shared relations in healthy adults. In this study, this goal was accomplished with a prospective data collection study which evaluated these relations based on the results from a narrowly-focused battery of traditional measures selected to specifically represent the same four domains as have been found in the computerized battery with clinical samples.

HYPOTHESES

Hypothesis 1

Traditional neuropsychological measures that are putative measures of specific cognitive domains will demonstrate significant intercorrelations with each other within the specified domains. The direction of the correlation may be positive or negative depending on the type of measure (e.g., as performance for the tasks improves measures involving completion time will be negatively correlated with measures involving raw number correct.)

A: The following measures of Attention will be significantly correlated - WAIS-III Digit Symbol raw score, Digit Span Forward total correct, and Trail Making Test Part A time to completion.

B: The following measures of Executive Functioning will be significantly correlated - WAIS-III Digit Span backward total correct, Paced Auditory Serial Addition Task (PASAT), Trials 1 and 2, raw score correct, and Stroop Neuropsychological Screening Test color-word time to completion.

C: The following measures of Memory will be significantly correlated - Rey Auditory Verbal Learning Test total correct (all trials) raw, WMS-III Verbal Paired Associates I and II total correct (all trials) raw, and WAIS-III Digit Symbol Incidental Recall total correct raw.

D: The following measures of Visuospatial Processing will be significantly correlated - WAIS-III Matrix Reasoning raw score, WAIS-III Block Design raw score, and WMS-R Figural Memory total correct.

Rationale

Using a traditional neuropsychological paradigm, it is common to have many tests that measure different aspects of the same neuropsychological construct (Lezak, 1995). Studies utilizing both traditional and computerized neuropsychological measures have found significant correlations between traditional measures designed to measure similar cognitive domain constructs (Kabat et al., 2001). However, before examining the comparability of traditional and computerized measures in evaluating shared cognitive domain constructs, it is important to first demonstrate the empirical interrelationships among traditional neuropsychological measures as related to the respective, expected cognitive domains they are purported to measure.

Hypothesis 2

Traditional and computerized measures that have been found to evaluate the same cognitive domains in clinical samples will significantly correlate with each other in healthy nonclinical adult samples.

A: Measures of Attention on the traditional battery (as described in Hypothesis 1 A above) will be significantly correlated with the throughput score on the WinSCAT code substitution learning task.

B: Measures of Executive Functioning on the traditional battery (as described in Hypothesis 1 B above) will be significantly correlated with the throughput scores on the WinSCAT mathematical processing and running memory tasks.

C: Measures of Memory on the traditional battery (as described in Hypothesis 1 C above) will be significantly correlated with the throughput score on the WinSCAT delayed code substitution task.

D: Visuospatial Processing on the traditional battery (as described in Hypothesis 1 D above) will be significantly correlated with the throughput score on the WinSCAT Match-to-Sample task.

Rationale

Previous research (Kabat et al., 2001; Bleiberg et al., 2000), utilizing regression analysis in clinical populations, demonstrated the predicative utility of computerized tests on traditional tests and cognitive domains. Ongoing research in normal populations (e.g., see Kane et al., 2005) indicates a similar pattern of findings.

Hypothesis 3

Computerized testing measures that evaluate specific cognitive domains will be found to significantly predict performance on composite measures of the respective cognitive domains in healthy adult samples. Because of the well-established relationship between general intellectual functioning and neuropsychological testing results, general intellectual functioning will be examined for inclusion as a covariate (Lezak, 1995). Additionally, because the computerized metrics are sensitive to differences in motor functioning, the results of a motor task will also be examined as a potential covariate.

A: The throughput score on the WinSCAT code substitution task will predict a composite measure of Attention from the traditional battery (based on the measures described in Hypothesis 1 A above).

B: The throughput scores on the WinSCAT mathematical processing task and the running memory task will each predict a composite measure of Executive Functioning from the traditional battery (based on the measures described in Hypothesis 1 B above).

C: The throughput score on the WinSCAT delayed code substitution will predict a composite measure of Memory from the traditional battery (based on the measures described in Hypothesis 1 C above).

D: The throughput score on the WinSCAT match-to-sample task will predict a composite measure of Visuospatial Processing from the traditional battery (based on the measures described in Hypothesis 1 D above).

Rationale

Previous research utilizing factor analysis (Kabat et al., 2001; Bleiberg et al., 2000) in clinical populations has identified three WinSCAT factors. Visuospatial processing has been postulated as an additional independent factor (Kane et al., 2005). Relationships between computerized measures and composite measures of the cognitive domains from traditional neuropsychological tests were expected to parallel the relationships between computerized measures and the individual traditional neuropsychological test measures of the domain.

Research Design and Methods

The purpose of this doctoral research project was to examine the relationships between select traditional and computerized neuropsychological measures. This study compared traditional and computerized neuropsychological measures in a newly collected data sample consisting of 75 physically and mentally healthy adults, with traditional neuropsychological tests that were chosen specifically for their relationship to cognitive constructs believed to be related to the WinSCAT measures. The WinSCAT analyses were based on the throughput score for each task (a measure of accuracy per unit of time). This score was chosen based on emergent data from newer studies of the WinSCAT indicating that the throughput scores are normally distributed, whereas the accuracy and response time measures (analyzed in previous studies) are not (Kane et al., 2005). Statistical analyses were completed with the Statistical Package for the Social Sciences software (SPSS for Windows, release 12.0.1). The USUHS institutional review board approval of this study is provided in Appendix D.

Study Procedures

Overview: IRB approval was obtained for the collection of additional data in healthy individuals age 18 and over, and a copy of the informed consent document for this study is provided in Appendix D. The targeted sample was recruited by newspaper ads and flyers from both the military (non-student) and civilian populations in the greater Washington, D.C., metropolitan area. Participants were told that the study's purpose was to examine the relationship between different types of paper-and-pencil and computerized neuropsychological tests. Exclusion criteria included conditions that may impact neuropsychological test performance including uncontrolled chronic medical problems (heart disease, high blood pressure, diabetes mellitus, osteoarthritis, other chronic joint, muscle, or nervous system disorder), past or current diagnosis with any neurological condition, current psychiatric diagnosis, history of head injury with loss of consciousness, or any condition adversely impacting motor coordination/motor skills (e.g., peripheral neuropathy). Non-military participants were compensated $30 for their time. All potential participants were screened by experienced or trained interviewers to determine their eligibility for participation. All individuals who met the initial inclusion criteria were invited to set up a time to complete the informed consent documentation and participate in the study.

The study involved the collection of data using traditional and computerized measures. All data were collected on forms that include a non-identifying code number. The master code list, connecting the non-identifying numbers with the subject specific demographics, was kept in a secured, separate location from the research data. Data were collected strictly for research purposes and not for clinical evaluation. If any significant

medical or psychiatric symptomatology had become evident during the study, then the subject was to be referred to a licensed psychologist (on the staff of USUHS) for further evaluation and, if deemed necessary, to other health care providers. Given the nature of the study, the inclusion criteria, and the screening process, it was believed the risk for such an event would be minimal. At the conclusion of the study, no subjects had displayed signs or reported symptoms that met the above criteria, and hence no subjects were referred for further evaluation.

Measures

Demographic Information: In accordance with the general recommendations of Lezak (1995) regarding the potential impact of contextual factors in neuropsychological assessment, standard background information was collected including the date of testing, age, gender, ethnicity/race, education completed, preferred handedness for writing, current medication use, previous experience with neuropsychological testing, the identification of the researcher conducting each examination, time of testing, and the location of testing. To control for the potential impact of subclinical seasonal affective disorder (a form of depression), general weather conditions (i.e., temperature, cloud cover, and precipitation) were recorded.

Traditional Neuropsychological Measures: The traditional neuropsychological measures used in this study were designed to specifically evaluate the cognitive domains that have been found to be related to the WinSCAT subtests in the research literature as well as in preliminary exploratory factor analyses. These cognitive domains are: attention, executive functioning, memory, and visuospatial processing. Based on discussions regarding the number of measures required to sufficiently evaluate the four

cognitive domains listed above, three measures were chosen per domain (Kane, personal discussion, 20 September 2003). In addition, the domains of general intellectual functioning and simple motor skills were measured for their potential use as covariates. The specific measures that were used in this data collection study included: the Shipley Institute of Living Scale, the Grooved Pegboard Test, the Rey Auditory Verbal Learning Test (RAVLT), the Trail Making Test, Parts A and B, the Stroop Color-Word Interference Test, the Paced Auditory Serial Addition Task (PASAT), one WMS - III subtest (Verbal Paired Associates), six WAIS - III subtests (Block Design, Matrix Reasoning, Digit Symbol/Coding, Symbol Search, Letter-Number Sequencing, and Digit Span), and one WMS-R subtest (Figural Memory). These traditional neuropsychological tests and their associated cognitive domains are presented in Appendix E, Tables 1.4 and 1.5.

Computerized neuropsychological measures: The WinSCAT battery of five computerized neuropsychological measures was administered. The WinSCAT tests are code substitution, running memory, mathematical processing, match-to-sample, and delayed code substitution. For all WinSCAT tests, the measures include one primary metric: the throughput score (a measure of accuracy in units of time). The WinSCAT was the computerized neuropsychological battery used in both the Pyridostigmine and L-Tyrosine studies, and the same tests administered in those studies were administered in this study. A list of the WinSCAT tests, and the cognitive domains related to each test, is presented in Appendix E, Table 1.2.

Subjects description: The study 2 sample consisted of 75 healthy, young to middle-aged, highly-educated adults, the majority of whom were female Caucasians. Subject demographic data for study 2 is presented in Table 17.

Procedures: Participants were recruited for participation in a 2-hour session comparing traditional and computerized neuropsychological measures by newspaper ads and flyers in the greater Washington, D.C., area. All potential participants were screened by the study investigator to determine their eligibility for participation (see Appendix F for telephone screen). All individuals who met the initial inclusion criteria were invited to set up a time to complete the informed consent documentation (ICD, Appendix D) and participate in the study. After completing the ICD, the enrolled subject was assigned a 4-character coded identifier (e.g., JA01) based on the chronological order of enrollment in the study (01 for the first enrolled subject). This coded identifier was used for labeling the data collection materials. No participant names were placed on any of the data collection forms. After receiving a coded identifier, the subjects were administered a brief developmental and history questionnaire (see Appendix G). If the participant was an employee at the USUHS, they were administered the USUHS employee volunteer form (see Appendix H). In order to control for the potential impact of test administration order, they were first administered either the traditional neuropsychological tests or the WinSCAT computerized test battery (even numbered participants were administered the WinSCAT first, while odd numbered participants were administered the traditional neuropsychological tests first.) Information on the WinSCAT test battery is presented in Appendix I. The participants were informed that the tests are for research purposes only and not to be used for clinical application or diagnosis. All procedures were administered

by the study investigator. Where possible, all procedures were completed in the Neurocognitive Laboratory, located adjacent to the USUHS cafeteria. However, if the participant was not able to travel to this location, the testing took place at a location of the participant's convenience. In this event, all efforts were be made to conduct the testing in a quiet, well-lighted location with minimal distractions. Any factors deemed to be potentially impactful on the testing by the examiner were noted in the subjects file.

Test Administration: The following traditional neuropsychological tests were administered in the order listed. Each of the tests was administered using the standardized instructions available in the formal documentation for these published and widely-used measures:

Neuropsychological Test Battery

10 minutes: Rey Auditory Verbal Learning Test (RAVLT)-I
5 minutes: Trail Making Test, Parts A and B
4 minutes: Digit Symbol/Coding (plus Incidental Recall)
7 minutes: Matrix Reasoning
3 minutes: Digit Span, Forward and Backward
5 minutes: Stroop Color-Word Interference Test
5 minutes: Rey Auditory Verbal Learning Test (RAVLT)-II
7 minutes: Block Design
6 minutes: Wechsler Memory Scale-III subtest (Verbal Paired Associates)-I
3 minutes: Symbol Search
5 minutes: Grooved Pegboard Test
3 minutes: Wechsler Memory Scale-R subtest (Figural Memory)
10 minutes: Paced Auditory Serial Addition Task (PASAT), Trials 1 and 2
3 minutes: Letter-Number Sequencing
2 minutes: Wechsler Memory Scale-III subtest (Verbal Paired Associates)-II
15 minutes: Shipley Institute of Living Scale (Verbal and Abstract Reasoning)
93 minutes total

The WinSCAT computerized test battery was introduced and a single operational trial was completed with brief oral instructions prompting at the beginning of each test. The instruction for each of the five tests was presented on the screen, followed by a brief

practice trial, before the actual test trial began for each task. The test administrator read the instructions out loud and provided any additional information or clarification needed to ensure understanding of each test's directions. The WinSCAT with on-screen instructions required approximately 20 minutes to complete. If, during the testing procedure, the participant required a short break, then it was accommodated at the next available between-test interval. Approximately half of the subjects took a break of 5 minutes or less at this point, and half did not take a break at all. At the end of the testing, a short rapport scale was administered (Appendix J). The elapsed time for this procedure, including reviewing the consent form, traditional neuropsychological testing, and computerized neuropsychological testing, was around 2 hours.

Data Collection: All data from the study were entered and analyzed on password-protected computers by the study investigator. All data entered were checked for accuracy at least one time prior to analysis.

Risks/Benefits

There were no foreseen risks for participation in this study, and no adverse events had occurred by the end of the studies. The procedure was short (approximately 2 hours) and civilian participants were compensated $30 for their time (uniformed participants are not eligible for financial compensation.) All were thanked for their participation and it was explained that their participation would contribute to the empirical literature and that their results may be used to help determine the appropriateness of the use of computerized neuropsychological measures in the future.

Data Analyses

As in study 1, this study employed bivariate correlations and multiple regression analyses to test the hypotheses. Bivariate correlations were used in the primary analyses to examine: 1) the relationships among the traditional neuropsychological measures that purportedly evaluate the same cognitive domains, and 2) the relationships between composite measures of those traditional domains with the WinSCAT tasks that have been found to represent those domains in clinical patient samples. Multiple regression is a general technique that is used in order to test the strength of relationships between multiple predictors and a single outcome measure (Cohen & Cohen, 1983), and is consistent with the existing analytic methodology employed in the scientific literature for evaluating the relationships between traditional neuropsychological measures and the computerized tests contained in the WinSCAT battery (e.g., Kabat et al., 2001; Bleiberg et al., 2000; Wilken et al., 2003). Given the ongoing efforts to establish the neurocognitive constructs tapped by the WinSCAT tests (e.g., Retzlaf & Vanderploeg, 1999), the examination of the extent to which the WinSCAT measures predict performance on traditional neuropsychological tests (and the well-established cognitive domains they measure) is warranted. All statistical analyses were completed with the Statistical Package for the Social Sciences software (SPSS for Windows, release 12.0.1).

As in study 1, the WinSCAT measure of interest in all present study analyses is the throughput score for each task. This score (which combines speed and accuracy) shows good normality of distribution as well as good stability, while scores of just reaction time or accuracy do not (Kane et al., 2005). Missing data for the traditional

neuropsychological data were handled with the pairwise deletion method, and with the listwise method for the WinSCAT data.

In order to test the overarching and sub-components of hypotheses 1 and 2, simple bivariate correlations were calculated and evaluated, crossing all of the traditional tests with each other (H1) and the traditional tests with the computerized neuropsychological measures (H2). The number of cognitive domains evaluated in both hypotheses 1 and 2 was four; this was based on the prospective nature of this study and its explicit intention of evaluating the four domains across traditional and the WinSCAT measures. This differs than the number of domains evaluated in hypotheses 1 and 2 of study 1, however, these differences in numbers of domains were not anticipated to impact the results of the analyses as the neurocognitive domains of interest for the WinSCAT (attention, executive functioning, memory, and visuospatial processing) were included in all hypotheses for both studies.

For hypothesis 3, the relationships of subject demographics, general intellectual functioning and dominant hand motor performance with the WinSCAT test measures were first evaluated using bivariate correlations, independent samples t-tests or between-groups ANOVA analyses as appropriate for the distribution of the variable. Any variable that was significantly related to any WinSCAT test was included in all regression analyses to control for contributions of that variable for identifying relationships between the WinSCAT test and its respective cognitive domain. The outcome measures (dependant variables) for the multiple regression analyses in hypothesis 3 were composite cognitive domain scores that were derived from the relevant individual traditional neuropsychological testing measures. The predictor variables were the respective

WinSCAT measures that are believed to represent the same cognitive domains as the traditional composite measures. The analyses used two-tailed tests, and the alpha level was set at $p<0.05$.

To create the outcome measures to be predicted by the WinSCAT measures in hypothesis 3, the traditional neuropsychological measures that evaluate each specific cognitive domain were combined into a standardized composite summary domain score that was an average of the contributing measures' standardized z scores (with each test being equally weighted). Standardized z scores for the contributing measures were created by subtracting each respective measure's mean score from each subject's raw score on that measure before dividing that difference score by the respective measure's standard deviation. This resulted in 4 z scores, one each for attention, executive functioning, memory, and visuospatial processing. The tests included in each domain for hypothesis three are shown in Appendix E, Tables 1.2. These measures were chosen for their measurement of the listed cognitive domains based on well-established relationships in the general clinical neuropsychological literature (Lezak, 1995), as well as in recent empirical literature on this topic (Wilken et al., 2003).

The regression models that were evaluated for hypothesis 3 first entered (as a block) those demographic variables that were significantly associated with any of the predictor WinSCAT measures with either statistical significance (t-test and ANOVA comparisons) or at $r = .3$ or higher (Pearson correlation analyses). These criteria were selected based on relationships found between demographic variables and the relationship between traditional neuropsychological tests and WinSCAT tests in the existing literature (e.g., Bleiberg et al., 2000). The measure of estimated general intellectual functioning

was then entered as the second step in the regression equation if it was shown to be significantly related to any of the WinSCAT measures in bivariate correlation analyses. This same procedure was applied to examine the potential inclusion of the measure of simple motor skills. The last step in the regression analysis was to enter the WinSCAT throughput measure of interest. In all regression analyses, the relevant cognitive domain z score was the dependant variable to be predicted from the model.

Power and Sample Size

As in study 1, the sample size calculations for this study were selected by using the findings of existing previous research (Bleiberg et al., 2000; Kabat et al., 2001) on this topic. In their clinical populations, they found statistically significant relationships between the traditional neuropsychological tests and the WinSCAT tests at the r = .20 to r = .30 level(s). In this study of normal subjects, a level of r = .40 is postulated as a conservative estimate of the expected magnitude of the correlation required to reach statistical significance. Given that assumption and an alpha level of .05, the estimated sample size needed for this study is 79 (NQuery Advisor Analysis Software). This sample size is consistent with the empirical literature examining the relationship between traditional and computerized neuropsychological measures (previously reviewed in the ANAM section), whose average sample size was 71.

Study 2 Results

Summary of Results Presentation

The primary hypothesis for study 2 was that traditional and computerized neuropsychological measures that have been found to be significantly related to each other in clinical patient samples would be significantly related in a prospectively collected data set that was specifically designed to evaluate the same relationships in a healthy adult sample. Three different primary hypotheses were proposed, and each primary hypothesis was further broken down by the specific tests and/or cognitive domain(s) being analyzed. In this study, the number of sub-hypotheses was four for hypothesis 1, four for hypothesis 2, and four for hypothesis 3.

The results are presented in the order of the hypotheses. Before hypothesis 3 is reported, the relationships of the demographic information with the primary predictor variables (WinSCAT throughput scores) are reported, for use as covariates in the analyses as appropriate when related to the predictors.

Hypothesis 1

Traditional neuropsychological measures that are putative measures of specific cognitive domains will demonstrate significant intercorrelations with each other within the specified domains. The direction of the correlation may be positive or negative depending on the specific measures being analyzed, but the expected direction was known a priori based on the purported relations among those variables measuring similar domains. As a result, all correlations were evaluated with one-tailed significance levels set at $p<.05$.

The final sample size on which valid data for the traditional neuropsychological test battery were available for analyses in hypothesis 1 (H1) was N=72. H1 was evaluated based on four sub-hypotheses (A-D), representing each of the four cognitive domains that had been found to be related in clinical patient samples. The cognitive domains that were evaluated with the traditional neuropsychological measures were attention (three measures), executive functioning (three measures), memory (three measures), and visuospatial processing (three measures). Of the total 12 intercorrelations among the four within-domain analyses, 12 (100%) were significant at $p<.05$ ($r \geq \pm.26$) (see Tables 18-21). Of these, 1 was of a small magnitude ($r \geq .10$ to $r <.30$), 8 were of a moderate magnitude ($r \geq .30$ to $r <.50$), and 3 were of a large magnitude ($r \geq .50$) (Cohen, 1988).

On the attention domain (H1:A, Table 18) the hypothesis was strongly supported and all measures were significantly intercorrelated with at least a moderate magnitude of the strength of the relationships ($p<.05$, $r \geq \pm.26$). On the executive functioning domain (H1:B, Table 19) the hypothesis was strongly supported and all measures were significantly intercorrelated with at least a moderate magnitude of the strength of the relationships ($p<.05$, $r \geq \pm.38$). On the memory domain (H1:C, Table 20) the hypothesis was strongly supported and all measures were significantly intercorrelated with at least a moderate magnitude of the strength of the relationships ($p<.05$, $r \geq \pm.35$). On the visuospatial processing domain (H1:D, Table 21) the hypothesis was strongly supported and all measures were significantly intercorrelated with at least a moderate magnitude of the strength of the relationships ($p<.05$, $r \geq \pm.36$).

Hypothesis 2

Traditional and computerized measures that have been found to evaluate the same cognitive domains in clinical samples will significantly correlate with each other in a healthy nonclinical adult sample and will show weaker correlations between traditional and computerized measures on theoretically different domains. The direction of the correlation may be positive or negative depending on the specific measures being analyzed, but the expected direction was known a priori based on the purported relations among those variables measuring similar domains. As a result, all correlations were evaluated with one-tailed significance levels set at $p<.05$.

As in study 1, validity of the traditional neuropsychological and WinSCAT measures was evaluated based on ranges (e.g., no accuracy percentages above 100 or below 60 if based on a dichotomous variable) and analyses were conducted using only subjects determined to have valid results. To ensure maximal data quality, if an invalid metric for a subject on any WinSCAT measure was found, that subject was excluded from further analyses for all WinSCAT measures. Invalid data on neuropsychological measures precluded use of that subject for the analyses involving the specific measure. The final sample size on which valid data were available on both the traditional neuropsychological test battery and all of the computerized measures for analyses in hypothesis 2 (H2) was N=72. H2 was evaluated with a total of four sub-hypotheses, representing four of the cognitive domains that were examined in H1. Thus, the cognitive domains that were evaluated from the traditional neuropsychological measures in H2 were attention (three measures), executive functioning (three measures), memory (three measures), and visuospatial processing (three measures).

Of the total 15 intercorrelations that resulted from the expected relations between each of the four traditional neuropsychological domain and each of the five computerized WinSCAT measures hypothesized to represent the respective domains (i.e., two WinSCAT tests were expected to relate to one traditional neuropsychological domain [yielding 6 correlations], and the remaining three WinSCAT tests were expected to relate to one traditional neuropsychological domain [yielding 9 correlations]), 13 (87%) were statistically significant at $p<.05$ ($r \geq \pm.21$). Of the 13 statistically significant correlations, 3 were of a small magnitude ($r \geq .10$ to $r <.30$), 8 were of a moderate magnitude ($r \geq .30$ to $r <.50$), and 2 were of a large magnitude ($r \geq .50$) (Cohen, 1988). On three of the four expected domains to have relationships with one or more of the computerized measures, all tests within that domain (i.e., executive functioning, memory, visuospatial processing) were significantly correlated with the expected computerized measure (i.e., mathematical processing [MTHTP], code substitution delayed memory [CDDTP], and match-to-sample [M2STP], respectively) ($p<.05$) (see Table 22).

Of the total 45 intercorrelations between the four traditional neuropsychological domain measures (attention, executive functioning, memory, visuospatial processing) and the specific computerized measures that were not expected to be related, 27 (60%) were statistically significant at $p<.05$ ($r \geq \pm.21$). Of the 27 statistically significant correlations, 10 were of a small magnitude ($r \geq .10$ to $r <.30$), 16 were of a moderate magnitude moderate ($r \geq .30$ to $r <.50$), and 1 was of a large magnitude ($r \geq .50$) (Cohen, 1988). Overall, of a total of 60 intercorrelations, significant correlations ($p<.05$) were found between the traditional neuropsychological measures and the computerized measures on 40 measures across all four of the domains (see Table 22).

Hypothesis 3

Computerized testing measures that are believed to evaluate specific cognitive domains will be found to significantly predict performance on composite measures of the respective cognitive domains from the traditional neuropsychological measures in healthy adult samples. Because of the well-established relationship of demographic variables and general intellectual functioning with neuropsychological testing results, these variables were examined for potential inclusion as covariates (Lezak, 1995). Additionally, because the computerized metrics are sensitive to differences in motor functioning, dominant hand performance on a speeded motor dexterity task was examined as a potential covariate.

Several contextual factors including time of testing, location of testing, handedness of participant, test administration order, and rapport with the examiner, were analyzed for their possible relationship with the WinSCAT throughput measures. None of these factors were found to have statistically significant relationships with the WinSCAT measures. Additionally, as in study 1, potential contributions of demographics, estimated intellectual functioning, and dominant hand motor dexterity speed scores to the predictor WinSCAT throughput scores were evaluated with bivariate correlations (age, estimated intellectual functioning, and motor speed), independent samples t-tests (gender and ethnicity), or analysis of variance (education). Based on several statistically significant findings between age and general intellectual functioning with WinSCAT measures, these factors were included as control variables in the regression analysis. Age (but not gender, ethnicity, or motor speed) was found to be significantly correlated ($p<.05$) with four of the five WinSCAT measures (code

substitution learning [CDLTP], running memory [RMTP], match-to-sample [M2STP], and code substitution delayed memory [CDDTP]). Estimated intellectual functioning was found to be significantly correlated ($p<.05$) with one of the five WinSCAT measures (mathematical processing throughput [MTHTP]) (see Tables 23a – 23e).

The final sample size on which valid data were available for the (H3) regression analyses was 72. There were a total of four sub-hypotheses (A-D), one for each of the four final cognitive domains. As in study 1, one of the cognitive domains (executive functioning) was hypothesized to have two different computerized measures as significant predictors. The predicted cognitive domain composite scores from the traditional neuropsychological measures were attention, executive functioning, memory, and visuospatial processing. The final analyses consisted of a three-block regression analysis for each predictor, with the significant demographic variable (i.e., age) entered as the first block, general intellectual functioning (i.e., Shipley score) in the second block, and the computerized test (the predictor of interest) as the third block. Results from the five analyses associated with each of the five WinSCAT predictor measures are shown in Tables 24 – 28.

On the attention domain (H3:A, Table 24), the hypothesis was not supported. The results of the three-block hierarchical regression indicated that the overall model was significant (adjusted $R^2 = 0.37$, $p<.05$). However, the code substitution learning task did not predict a significant amount of the variance on Attention test performance after contributions from the control variables were accounted for (R^2 change = 0.01, $p>.05$). On the executive functioning domain (H3:B, Tables 25 and 26), the hypothesis was supported for one WinSCAT task and was not supported for the other WinSCAT task.

The results of the three-block hierarchical regression indicated that the overall models were significant for both analyses. On the mathematical processing task (Table 25), the overall model was significant (adjusted $R^2 = 0.37$, $p<.05$) and the mathematical processing task was statistically significant and of a moderate magnitude in predicting a significant independent amount of the variance on Executive Functioning test performance after the other control variables were accounted for (R^2 change = 0.10, $p<.05$). On the running memory task (Table 26), the model was significant (adjusted $R^2 = 0.26$, $p<.05$) but the running memory task did not predict a significant amount of the variance on Executive Functioning test performance after accounting for the control variables (R^2 change = 0.00, $p>.05$). On the memory domain (H3:C, Table 27), the hypothesis was supported. The results of the three-block hierarchical regression indicated that the overall model was significant (adjusted $R^2 = 0.50$, $p<.05$). In addition, the code substitution delayed memory task was statistically significant and of a small magnitude in predicting a significant amount of the variance on Memory test performance after the control variables were accounted for (R^2 change = 0.04, $p<.05$). On the visuospatial processing domain (H3:D Table 28), the hypothesis was supported. The results of the three-block hierarchical regression indicated that the overall model was significant (adjusted $R^2 = 0.58$, $p<.05$). In addition, the match-to-sample task was statistically significant and of a small magnitude in predicting a significant amount of the variance on Visuospatial processing test performance after the control variables were accounted for (R^2 change = 0.03, $p<.05$).

Discussion

Based on the results of study 2, in a healthy, high-functioning adult sample, significant relationships were found to exist between traditional and computerized neuropsychological measures that purport to test performance in similar cognitive domains. As with study 1, even when controlling for many potential variables that could have impacted WinSCAT performance, most of these hypothesized relationships remained. The findings on this prospective data set provide partial support for all three primary hypotheses.

In hypothesis one, the traditional neuropsychological measures chosen to represent specific cognitive domains were found to strongly relate to each other. The lowest (albeit significant) within-domain correlation found between test measures was within the attention domain and involved the tests of the Digit Span forward test with the Digit Symbol Coding ($r = .26$). All other relationships were significant at the $p<.05$ level, and varied between r's of .35 (Verbal Paired Associates with Digit Symbol Incidental Learning) to .67 (Block Design with Matrix Reasoning). This fairly wide range of relationships is not surprising. The tests were chosen for their ostensive capacity to form (when combined) a general cognitive domain index score. Some of the tests used to form domain scores were themselves taken from test batteries where they are combined for the determination of higher order cognitive functioning (e.g., Block Design and Matrix Reasoning are two of the three tests used to test Perceptual Organization in the WAIS-III test battery.) Other tests used to form domain scores are not used together in standardized test batteries and were chosen (in part) for the different performance requirements the tests elicit. For example, the Paced Auditory Serial Addition Test

(PASAT) combines the requirements of auditory information processing speed and calculation ability in an implicitly time-pressured, N-back working memory paradigm. In contrast, the Stroop Neuropsychological Screening test, Color Word task, requires cognitive flexibility and response inhibition in an explicitly timed format.

In hypothesis two, the selected traditional neuropsychological tests that represented the cognitive constructs of interest were generally found to correlate with the WinSCAT measure of the same cognitive domain, and to correlate less with other domains (see Table 22). However, as with study 1, there were some notable exceptions to this general finding.

In the expected correlations between the traditional neuropsychological tests (organized by cognitive domain) and the computerized measure hypothesized to represent the same domain, only two tests (Digit Span forward and Digit Span backward) did not have a statistically significant relationship. This brought into question the validity of the Digit Span task results. One way to analyze this possibility was to see if the Digit Span tasks related to each other in a consistent manner when compared to other studies involving the relationship of the two Digit Span tests (i.e., forward and backward). In our sample, the correlation between Digit Span Forward and Backward was $r = .55$. This is very consistent with their correlation of $r = .60$ in the WAIS-III standardization sample (Tulsky, Saklofske, & Zhu, 2003). Another possibility was that the use of total raw scores (vice maximum span scores, as used in study 1) somehow adversely impacted the results. In a post-hoc analysis, we analyzed Digit Span forward and backward maximum span scores and found no significant differences in results. Thus, based on the evaluation of the above factors, it appears the results of the Digit Span tests are valid.

One possibility regarding the unexpected findings on the Digit Span task is that it appears to involve a two-step performance process, with step one primarily involving sustained attention and auditory encoding, and step two involving recall, manipulative sequencing, and vocalization of the information (Bannatyne, 1974). Varying performance on these two steps in the diverse population of study 2 (as opposed to the more homogeneous population of study 1) may account for the unexpected Digit Span test results. For example, this subject population may load on either the requirements of the first step or second step of the Digit Span task, while the study 1 population may load relatively more on the requirements of only the second step, because of their age and educational background of the high functioning sample in study 1. This would result in different cognitive processes producing the same outcome on the Digit Span task in studies 1 and 2, and attenuate relationships between this task and other measures. This difference could at least partially explain the between-study differences found on the relationships of the Digit Span measure with the WinSCAT test.

Another noteworthy finding apparent when looking at the results in Table 22 is the number of significant relationships between some of the WinSCAT measures and the traditional neuropsychological measures. In some cases there were many significant correlations between a WinSCAT measure and many traditional neuropsychological measures, both within the cognitive domain they were hypothesized to be related to as well as with measures they were not hypothesized to be strongly related to. For example, the WinSCAT code substitution learning task (CDLTP) was found to have statistically significant relationships with eleven of the twelve total traditional neuropsychological tests (see Table 22). This is somewhat similar to the results of study 1, where 36% of the

traditional neuropsychological tests had statistically significant relationships with the CDLTP task at the $p<.05$ level, and where the CDLTP task had the most significant relationships with non-hypothesized measures on the traditional neuropsychological tests (see Table 10). One interpretation of these findings is that the CDLTP task has a multiplicity of performance characteristics (including general attention, learning, visuospatial processing, symbol manipulation, and processing speed) and that these requirements are sufficiently diffuse so as to make characterizing the CDLTP task as evaluating a unitary cognitive construct (e.g., attention), overly simplistic especially in this markedly heterogeneous sample.

Despite the problem outlined above, the expected positive relationships were much stronger then the expected weaker relationships. For example, of the correlations that were expected to be related, 67% were significant at the $p<.05$ level. With the correlations not expected to be related, only 38% were significant at the $p<.05$ level. This difference, combined with the findings in hypotheses 1, increased our confidence that we had constructed cognitive index scores that were both valid and that related to the expected WinSCAT measures.

In hypothesis three, the five WinSCAT measures that were predicted to significantly relate to the respective traditionally-derived cognitive indexes were found to do so for all four predicted domains (for the entire model). However, as with study 1, only three of five independent analyses were significant. Specifically, the WinSCAT CDLTP task did not independently predict performance on the attention domain score after controlling for potential contributions from non-specific demographic and intellectual ability factors (see Table 24). Additionally, the WinSCAT RMTP task did

not independently predict performance on the executive functioning domain score after controlling variables had been entered (see Table 26).

The non-significant findings on the attention domain are not surprising when considering the information presented in Tables 22 and 24. In Table 22, the Digit Span forward test was found to have almost no relationship to the CDLTP task ($r = .08$). This undoubtedly reduced the strength of the relationship between the CDLTP task and the attention domain score (of which the Digit Span forward task formed 33% of the 3-test attention index score). As presented in the regression findings listed in Table 24, the demographic variable of age was found to account for 73% of the variance of the total model (i.e., adjusted R^2 of 27% of the total adjusted R^2 of 37%). This, combined with the significant correlation of $r = -.61$ between age and the WinSCAT CDLTP task (see Table 23a), suggests that performance on both the traditionally-derived attention index domain score and the WinSCAT CDLTP task is significantly related to the age of the participant. This is consistent with the general neuropsychological literature on the inverse relationship of age and performance on neuropsychological tests not related to verbal knowledge (e.g., Tulsky et al., 2003).

The non-significant findings on the executive functioning domain (for the WinSCAT running memory task) are also explained when analyzing the findings in Tables 22 and 26. The RMTP task was found to have more significant correlations with four traditional neuropsychological tests of other domains (Digit Symbol Coding, Block Design, Trail Making Test part A, and Matrix Reasoning) than with the tests of executive functioning (i.e., Digit Span backward, Stroop Neuropsychological Screening test, Color Word, and the Paced Auditory Serial Addition Test) [see Table 22]). As can be seen in

Table 26, the test of intellectual functioning (the Shipley Institute of Living Scale; Zachary, 1996) accounted for almost all of the performance on the executive domain index. This is somewhat surprising in that the Shipley test is not timed and the WinSCAT running memory task has a significant response-time component. However, this apparent relationship between the Shipley and the RMTP task could be explained in several ways. For example, the RMTP is perhaps the most difficult of the five WinSCAT tasks. The accuracies on this task are generally lower than on the other WinSCAT tasks (along with the WinSCAT memory task), and the response time requirements are the most intense because of the fast ongoing rate of stimulus presentation in the task. This forced reaction time component results in the RMTP having significantly faster response times than on the other WinSCAT tasks (e.g., in study 2, the median response time for the running memory task was .578 seconds, compared to 2.16 seconds for the mathematical processing task.) Subjectively, many subjects comment that the running memory task is the most difficult of the WinSCAT tasks. The intense performance requirements of the running memory task may make it be better suited for individuals of relatively higher intellectual aptitude, and the Shipley test may be providing a general measure of this aptitude. Alternatively, the Shipley and the WinSCAT running memory task may share significant variance on one (or several) cognitive construct(s), and as a result the inclusion of the Shipley as a covariate in the regression model may result in a significant loss of predictive power of the WinSCAT running memory task on executive functioning domain functioning.

Limitations

As with study 1, several limitations to this study are noteworthy. While this population differs from that of study 1 by being generally older, less physically fit, and primarily female, it is still not representative of the general population. For example, almost 75% of the subjects had at least a four-year college degree, and 34% had some type of graduate education. This compares with recent United States population statistics of 25% and 9%, respectively (U. S. Census Bureau, 2000). Given the known relationships between educational achievement and neuropsychological test performance, it is unlikely the results of this study are representative of the general population.

In this study the determination of medical history, psychiatric history, and current psychological conditions was completely based on self-report. This is different than in study 1, where an extensive medical evaluation was completed. We attempted to minimize the potential for inclusion of subjects who should have been excluded by screening at two different occasions, once during the initial phone or e-mail contact and again at the beginning of the testing procedure. However, the possibility exists that subjects were included who should have been excluded. The empirical literature on patient's reporting of their medical conditions indicates that they often fail to report significant conditions, including comorbid medical conditions and depression (Klabunde, Reeve, Harlan, Davis, & Potosky, 2005).

Another possible limitation to this study is that three tests were used to create each cognitive domain. While this seemed to be minimally sufficient for our purposes, it is possible that the use of three tests to evaluate cognitive domains resulted in a lack of comprehensive coverage of that domain. We attempted to maximize the coverage of the

domains by including tests with different performance elements (e.g., attention tests that involved motor skills, visual-spatial tracking, sequencing, auditory processing, etc), as well as by including tests with varying scoring requirements within each domain (e.g., tests with scoring of total correct and tests with scoring of time to completion). However, when operationalized broadly, general cognitive domains (e.g., attention) are inherently multifaceted, and using three tests per domain may have resulted in a lack of comprehensive coverage of the domains.

Another potential limitation relating to the domain index scores is that the three tests comprising each domain were equally weighted when creating the domain index scores. Given the exclusively visual presentation of the WinSCAT measures, and the requirement of all WinSCAT to answer the questions as fast and as accurately as possible, it may have been appropriate to give more weight to visually-presented tests, or to tests with a time performance factor (or tests that have both), and less weight to auditory tests, or tests that were not timed. In both the attention and executive functioning domains, this would have resulted in index scores that more closely related to the WinSCAT measures hypothesized to measure them by attenuating the impact of the measures that more weakly correlated with the WinSCAT measures (i.e., Digit Span forward and backward; see Table 22).

As in study 1, the data analytic technique in the regression portion of this study was designed to covary out variables, including education and intellectual functioning. This was again done to statistically adjust for the possible impact of spurious variance due to varying intellectual functioning. However, given the high education and intellectual functioning in this population (estimated total full-scale intelligence of 119.4,

SD = 8.0), this technique may have again reduced variance without correspondingly increasing the meaningfulness of the data.

In study 2 (in contrast to study 1), the WinSCAT tests were completed with an integrated keyboard-style touchpad mouse. While this may have had no impact on the results, we have no way of knowing this with any degree of certainty. It is interesting to note that the reaction times achieved in study 1 (using a standard computer mouse) were consistently faster than the reaction times in study 2 (using the keyboard touchpad mouse). This difference was slight (averaging around 5-10%), and may be completely accounted for by the different study subject demographics (e.g., study 1 had a higher percentage of males, study 1 participants were younger, etc). Therefore, it is possible that the combined differences in both the demographics and the response method to the WinSCAT measure may have created differences in the findings between studies 1 and 2.

OVERALL SUMMARY AND GENERAL DISCUSSION

This project was designed to evaluate the construct validity of the WinSCAT performance assessment battery in a nonclinical adult sample. The primary purpose was to establish the neurocognitive content structure of the WinSCAT tasks, and to determine the applicability of the WinSCAT tasks to assess neurocognitive functioning. Statistical methods were used to analyze the relationship between a wide range of traditional neuropsychological tests and the tests of the WinSCAT computer battery. Unlike other previous studies on this topic, we sought to do this in healthy, adult samples. We utilized both an existing and a prospectively-collected data set.

Previous research has identified three neurocognitive domains (attention, executive functioning, and memory) that are represented by the five tasks comprising the WinSCAT battery when evaluated in clinical samples (Kane et al., 2005). Additionally, the domain of visuospatial processing has been postulated as a possible independent domain (Kabat et al., 2001). One of the major weaknesses with all of the previous research analyzing the construct validity of the WinSCAT is that they used either clinical populations or they did not screen out conditions (e.g., history of concussions, ADHD, etc) that can impact neuropsychological testing results. These studies also commonly used WinSCAT metrics (e.g., accuracy) that have been found to have non-normal distributions, in contrast to efficiency scores (e.g., throughput) that are normally distributed (Kane et al., 2005). We evaluated WinSCAT performance using the throughput scores in two different studies, both of which had nonclinical, healthy, adult subject samples. In one case (study 1), the traditional neuropsychological tests were not specifically chosen for their relationship to the WinSCAT tests, while in the other (study 2), the traditional neuropsychological tests were chosen prospectively for the purpose of evaluating the theoretical cognitive constructs in the WinSCAT. The number of cognitive domains evaluated in study 1 hypotheses 1 was eight and for hypothesis 2 was six. While this was different than the number of domains evaluated in hypotheses 1 and 2 in study 2, these differences in the numbers of domains was not anticipated to impact the results of the analyses as the neurocognitive domains of interest for the WinSCAT (attention, executive functioning, memory, and visuospatial processing) were included in all hypotheses for both studies. In both cases, several WinSCAT tests were found to have significant relationships with the cognitive domains they have been associated with in

clinical populations. This finding was the most robust with the WinSCAT memory and mathematical processing tasks, and less so with the WinSCAT match-to-sample, code substitution learning, and running memory tasks.

The overall findings of the present research project (studies 1 and 2) indicate that the WinSCAT is a valid measure of memory (across a heterogeneous sample of healthy adults) in comparison with the gold standard assessment of memory provide by traditional neuropsychological tests. In addition, and again in relation to traditional neuropsychological tests, the WinSCAT meaningfully assesses attention and executive functioning. More specifically, attention and executive functioning represent general cognitive processes that are requisite functions for all higher-order cognitive functioning skills (e.g., memory, visuospatial processing). In the present research project, the throughput measure was selected as the measure of interest because of its established normal distribution, in contrast with the other potential WinSCAT outcome measures of accuracy and reaction time. However, based on the existing WinSCAT research, the throughput measure is itself a measure of processing efficiency, which is directly impacted by functioning in the attention and executive functioning domains. Thus, those two overarching cognitive processes (i.e., attention and executive functioning) are represented in all five WinSCAT tasks. To summarize, the WinSCAT appears to be a valid and sensitive measure of the cognitive processes of attention, executive functioning, and memory, which are the three primary cognitive domains most vulnerable to disruption from even mild neurological injury (Vanderploegg, Curtiss, & Belanger, 2005).

Knowledge of the utility of the WinSCAT in clinical populations and the NASA astronaut population has been expanded by this study. The use of the WinSCAT for repeated measures assessment of memory functioning in both healthy and clinical populations appears to be supported by studies 1 and 2. The use of the remaining WinSCAT tests to evaluate the specific cognitive domains of attention, executive functioning and visuospatial processing, either in a one-time or repeated measure paradigm, is not directly supported by the findings in this research.

Additionally, there may be limitations to the utility of the WinSCAT battery in particular situations. For example, certain clinical populations may have conditions (e.g., Parkinsonism) that impact their motor functioning such that the use of the WinSCAT (which requires normal fine motor functioning) may not be indicated. Likewise, in a very high-functioning population with uniformly high intellectual functioning (e.g., astronauts), the use of the WinSCAT to discretely measure specific cognitive domains may not be indicated. However, given the high reliabilities of the WinSCAT measures (Kane et al., 2005), the use of the WinSCAT for within-subject repeated measures assessment of cognitive functioning in an astronaut population (as it is currently used) is not contraindicated by the results of the present research evaluating the specific cognitive domains at the first administration of the WinSCAT battery.

A more general finding of the studies is that the WinSCAT battery may not be better suited than traditional neuropsychological tests for the one-time assessment of specific cognitive domains of functioning. Given the brevity of the WinSCAT (around 20 minutes) and the fixed modality of administration (visual processing with a fine-motor response), the failure of the instrument to effectively assess discrete cognitive domains

other than memory is not surprising. However, while not specifically addressed in studies 1 and 2, the use of the WinSCAT for repeated measures assessment of cognitive functioning may represent its greatest utility and greater benefit over traditional neuropsychological assessment practices. For example, repeated measures assessment of cognitive functioning (in either a clinical or high-functioning population) may be more parsimoniously achieved with the WinSCAT battery then with traditional neuropsychological measures.

The extent to which we met our project goals varied greatly. As can be seen in the results and discussion sections of studies 1 and 2, expanding the knowledge base of the relationships between traditional neuropsychological tests and the WinSCAT tasks has been largely accomplished. A total of 27 different traditional neuropsychological measures were administered across the two studies with all of the WinSCAT measures. Our knowledge of the relationships between specific neuropsychological tests and specific WinSCAT tasks, as well as factors that moderate this relationship (e.g., demographic variables), has been greatly expanded.

Knowledge of the neurocognitive content structure (relative to traditional neuropsychological tests) of the WinSCAT has been expanded by this project. Combined across both studies that made up this project, the WinSCAT memory task was found to significantly correlate with 79% (11 of 14) of the traditional neuropsychological tests of memory, which represent the gold standard for neurocognitive assessment. Additionally, the WinSCAT memory measure independently predicted memory performance on an index score of traditional neuropsychological tests of memory in both studies 1 and 2. Importantly, the traditional neuropsychological memory tests that comprised the

composite memory domain measures for the two studies did not overlap at all, which would seem to strengthen the claim that the WinSCAT memory test does actually test memory.

Complicating the construct structure picture are the conflicting findings on the other WinSCAT tasks between the two studies. All of the other four WinSCAT tasks (except for the memory task) were independent significant predictors of cognitive domain performance on only one of the two studies in this project. Of these four remaining tasks, the results of the WinSCAT mathematical processing task are the most similar between the two studies. In study 1 the mathematical processing task (hypothesized to independently significantly predict performance on a composite measure of executive functioning) had a trend towards significance ($p = .08$), and in study 2 it was a significant predictor. Strengthening our confidence in attributing executive functioning performance to the WinSCAT mathematical processing task are the study 2 findings, where this task was highly related to the chosen traditional tests of executive functioning and not very strongly related to the other tasks. Additionally, in clinical studies of the WinSCAT, performance on the mathematical processing task has been found to be significantly related to traditional tests of executive functioning and working memory (e.g., TMT B, Consonant Trigrams, and the PASAT, Bleiberg et al., 2000; WAIS-R Arithmetic, TMT B, Digit Span backward; Kabat et al., 2001).

The three remaining WinSCAT tasks, the code substitution learning task, the running memory task, and the match-to-sample task, also all had conflicting findings between studies 1 and 2. Based on the results of both studies, the code substitution learning task appears to be significantly impacted by age, and to a lesser degree by

education, and subject response speed/reaction time. These findings are consistent with the clinical neuropsychological literature on the impact of various demographic factors on performance of learning and attention tests (Lezak, 1995).

However, there also appears to be comparability between the findings on the WinSCAT memory task and the WinSCAT code substitution learning task. This would be expected, as they involve different aspects of the same task. A review of the information looking at the relationships of various factors between the WinSCAT memory task and WinSCAT code substitution task is particularly revealing. For example, when analyzing the relationships between these two WinSCAT tasks and demographic factors in study 2, along with general intellectual functioning, motor speed, and traditional neuropsychological tests, the findings are very similar (see Tables 22, 23a, and 23e). This may seem to indicate that the learning (i.e., code substitution) and recall (i.e., memory) WinSCAT measures are essentially accounting for similar shared variance and thus measuring the same cognitive construct.

It should be noted that the shared variance model is subject to limitations, especially as relates to tests of learning and memory (e.g., the WinSCAT code substitution and memory tests; [Delis, Jacobson, Bondi, Hamilton, & Salmon, 2003]). For example, factor analytic studies of various measures of traditional neuropsychological learning/memory tests show that they typically load on a single general memory factor (Wechsler, 1997). However, the clinical neuropsychological evaluation of memory function in clinical populations commonly includes evaluating for differences between performances on immediate recall, delayed recall, and recognition tasks and, when found, these differences can have significant diagnostic implications. In

summary, the relationship of the WinSCAT code substitution task with the WinSCAT code substitution delayed memory task (as demonstrated by analyzing their relationships with other factors) may itself be an important evaluative feature of the WinSCAT.

The WinSCAT running memory task was a significant predictor of an index of executive functioning performance in study 1 but not study 2. Based on the results of both studies, running memory task performance appears to be significantly impacted by age, education, and general intellectual functioning. As mentioned in the study 2 discussion section, the running memory task may be one of the most difficult in the WinSCAT battery. This may be why the general factors of age, education, and general intellectual functioning, all of which can impact general test performance, are accounting for a great deal of the performance on both the WinSCAT running memory task as well as the executive functioning domain score. Interestingly, in studies 1 and 2, there were significant correlations between traditional neuropsychological tests of both attention and executive functioning (see Tables 10 and 22). While speculative, it is possible that the WinSCAT running memory task measures cognitive performance at the intersection of the attentional and executive functioning systems (e.g., the attentional executive system and the executive motor response system; Andrewes, 2002), and that this may account for the relationships with tests of both attention and executive functioning.

Consistent with this assessment, in a prior factor analytic study of the WinSCAT, the running memory task was found to load on a "working memory/complex attention" factor (Kabat et al., 2001, p. 504), which could also be consistent with the central executive function within one widely used working memory model (Baddeley, 1986). Also, in a study on the impact of concussion on ANAM test performance, the running

memory task (which is the same on the ANAM as the WinSCAT) was found to be impaired at post-concussion day 4 (Warden, Bleiberg, Cameron, Eckland, Walter, et al., 2001). The study authors characterize the concussed subjects' deficits as related to impaired functioning of attention and concentration. Additionally, in both studies 1 and 2, the overall regression model for the running memory task was significant and accounted for exactly 26% of the variance in executive functioning domain performance. This finding is especially significant given the differing population demographics of studies 1 and 2.

The WinSCAT match-to-sample task was a significant predictor of an index of visuospatial processing performance in study 2 but not in study 1. The demographic variable of age was significantly related to match-to-sample performance, but only in study 2. This finding is not surprising given the greater variability in subject ages in study 2 (i.e., mean age of 36 years and a standard deviation of 15 years, vice a mean age of 29 years and a standard deviation of 6 years in study 1). The finding in study 2 was significant and negative ($r = -.44$) and, in a post hoc analysis, seemed to demonstrate a generally linear relationship. While WinSCAT task performance was better in study 1 on all tasks, the match-to-sample task demonstrated the greatest difference (around 15%) of all WinSCAT tasks. Besides age, this finding also seems to be related to gender, as males (who formed 70% of the study 1 population, vice 38% in study 2) had faster reaction times on the match-to-sample task compared to females by approximately 20%. Previous studies of the WinSCAT have had differing findings regarding the match-to-sample task. In one case it was found to load onto a working memory/complex attention factor (Kabat et al., 2001) while in another it was found to load onto a general memory

factor (Bleiberg et al., 2000). It may also be related to a more general visual working memory performance factor, as has been found to influence performance on the MicroCog computerized assessment battery (Stewart, 1998). However, in study 2, where specific, prospectively-chosen measures of visuospatial processing were included, it appears the match-to-sample task was most related to visuospatial tasks (with lesser relationships with measures of complex attention and memory; see Table 22).

There exist several inherent difficulties with evaluating the construct validity of specific neuropsychological tests designed to evaluate cognitive domains. As in the previous studies on the construct validity of the WinSCAT, in this project the cognitive constructs being evaluated were all operationalized in an orthogonal manner (i.e., characterizing each neuropsychological test used as belonging to one, and only one, domain). However, this mutually-exclusive approach to evaluate cognitive domains, while methodologically necessary, is also an oversimplification. For example, without adequate functioning in the attention domain, poor performance on a wide variety of neuropsychological tests would be expected on tests of attention and on tests of memory, executive functioning, visuospatial processing, etc. While in the clinical neuropsychological arena the impact of this issue can be evaluated and/or attenuated by the use of integrated, dynamic heuristics of brain function (e.g., the three principal functional units of the brain; Luria, 1973), or by the qualitative analysis of patterns of errors on neuropsychological tests (e.g., Kaplan's Boston Process approach; White & Rose, 1997). In research, such complex models are rarely used in lieu of the more popular nomothetic methodology.

Another major difficulty evaluating the construct validity of specific neuropsychological tests designed to evaluate cognitive domains is the multifaceted nature of the domains themselves. For example, the cognitive domain of attention includes a wide variety of elements including arousal, selectivity, focus, vigilance, shifting, distractibility, and intensity modulation (Mirsky, Anthony, Duncan, Ahearn, & Kellam, 1991). Even when these factors are reduced and/or combined to achieve a system level heuristic, attention remains a multifaceted construct. For example, one basic conceptualization of attentional structure posits four different, dynamically interacting systems (arousal, orienting, perceptual, and executive; Andrewes, 2002). In the clinical neuropsychology field, this issue is primarily addressed by utilizing a variety of tests, preferably of mixed administration modality, so as to address the heterogeneity of the domain being evaluated. Another manner in which this is addressed is by behavioral observations of the individual being evaluated during the assessment and testing sessions. However, these approaches do not lend themselves to the research arena owing to time/resource limitations, the nomethetic approach to neuropsychological research, and the difficulties of quantifying qualitative behavioral data within the testing context.

A subtle example of the above problem is illustrated in the memory domain index of study 2. The three tests chosen to comprise this domain (i.e., the Rey Auditory Verbal Learning test, the WMS-III Verbal Paired Associates test, and the WAIS-III Digit Symbol Incidental Learning test) were all chosen for their appropriateness in testing the cognitive domain of memory (Lezak, 1995). Additionally, because of the specific requirements of the task, the Digit Symbol Incidental Learning test was included because it was thought to include a strong visual memory component. This test was thought to be

an important factor to include because of the visual nature of all WinSCAT tasks (including the memory test), and balance against the purely auditory nature of the two other memory tasks. However, even with this completely non-auditory task, the Digit Symbol test has been found to correlate more strongly with auditory memory indexes than with visual memory indexes (Joy, Kaplin, & Fein, 2003). Thus, regardless of the factors that are included in the neuropsychological test decision-making process, it is difficult (if not impossible) to fully account for all of the possible factors that may impact the extent to which one is able to test different elements of neurocognitive functioning.

In summary, the present research has contributed to the limited existing empirical literature on the relationship between a specific computerized neuropsychological battery (the WinSCAT) and a wide variety of traditional neuropsychological tests. The combined findings of the archival and prospective studies provide insight into the factors that should be considered when choosing whether to utilize the WinSCAT or traditionally-administered neuropsychological tests. In situations that require a repeated measure paradigm of subtle changes in general neurocognitive functioning, the WinSCAT may prove superior to a more traditional neuropsychological battery. However, in situations where a comprehensive, one-time assessment of a broad array of discrete cognitive domains is desired, a traditional neuropsychological battery is likely to be more effective than the WinSCAT, which appears to only assess the memory domain reliably. In certain circumstances the use of both methods in a complimentary fashion may be indicated. For example, in a traumatic brain injury scenario, a traditional neuropsychological battery could be used to comprehensively assess the extent and

nature of cognitive impairments, while the WinSCAT could be used in a repeated measure fashion to monitor global neurocognitive recovery.

Future Directions

This is the first study that we know of that examines the relationship of the WinSCAT tests to traditional neuropsychological tests in a healthy adult population. It was designed to build upon and extend the existing and growing literature on computerized neuropsychological testing batteries. However, given the limitations in this study, several improvements for future studies examining the WinSCAT are indicated.

Future studies would benefit from an a priori approach to the selection of traditional neuropsychological test measures. While in this project one of the two studies utilized prospective test selection, in the other study the tests were not specifically chosen for their relationship to the cognitive domains of interest in the WinSCAT. It should be noted, however, that the tests used in the archival portion of this project are widely used, empirically validated, and appropriate for the requirements of the specific research projects in which they were used. Relatedly, the construct validity of the WinSCAT measures would benefit from being compared with cognitive domain scores created from a larger set of traditional neuropsychological tests. Additionally, with the strong reaction time requirement for all WinSCAT measures, it may be most appropriate to exclusively choose to compare them with traditional neuropsychological tests that are timed.

Standardized administration of the WinSCAT tests beyond the onscreen instructions in future studies should result in both increased available data due to increased uniformity of test instruction procedures, as well as decreased variability in WinSCAT performance secondary to differential examiner presence effects. While this

was done in study 2, it was not done in study 1. This strategy would increase the confidence of the findings of the relationships between the specific WinSCAT test and the cognitive construct(s) they are purported to test.

Further exploration of the impact of rapport on testing results should be explored. A rapport scale was used in study 2 to evaluate if that factor would have an impact on the relationships between traditionally-administered neuropsychological tests and the WinSCAT battery. In that study it was not found to be significantly related to the testing results. However, a single examiner completed all of the assessments and many of the subjects were known to the examiner, which may have introduced a positive bias into the self-report rapport instrument (range 0-10, mean 9.5, SD = .75). Future research in this arena should continue to evaluate the impact of this factor on testing results by including multiple examiners and participants who are unfamiliar with the examiners.

Future studies of the WinSCAT that utilize a more heterogeneous population would be valuable. In theory, if tests of the WinSCAT evaluate specific cognitive domains of functioning, then it will do so in a wide variety of subjects. However, ceiling and floor effects may become apparent with a sufficiently heterogeneous subject population. Research of this type could help define the possible limitations of extrapolating WinSCAT performance onto traditional cognitive domain functioning. Relatedly, and consistent with the recent recommendation of Kane et al. (2005), future studies evaluating the WinSCAT performance of very high-performing subjects (i.e., those comparable with the astronaut population for which the WinSCAT was developed) should be conducted. In addition, the WinSCAT should be integrated into emerging

technologies that are designed to proactively assess astronaut cognitive functioning (e.g., Genik, Green, Graydon, & Armstrong, 2005).

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APPENDIX A

Traditional neuropsychological tests administered in the Pyridostigmine and L-Tyrosine studies (Study 1) (with approximate administration time)

15 minutes: Shipley Institute of Living Scale (Verbal and Abstract Reasoning)
30 minutes: Wechsler Adult Intelligence Scale-III subtests
(Information, Digit Span, Similarities, Letter-Number Sequencing, Picture Completion, Matrix Reasoning, Symbol Search)
15 minutes: California Verbal Learning Test
10 minutes: Rey-Osterrieth Complex Figure Test copy, 3-minute, and 30-minute incidental recall trials
5 minutes: Trail Making Test, Parts A and B
5 minutes: Stroop Color-Word Interference Test
10 minutes: Wechsler Memory Scale-III subtests
(Logical Memory I & II, Family Pictures Test I & II)
7 minutes: Controlled Oral Word Association Test (FAS & Animals)
10 minutes: Wisconsin Card Sort Test
5 minutes: Grooved Pegboard Test

APPENDIX B

Pyridostigmine Informed Consent Document, IRB approval, and permission to use data

RESEARCH STUDY: Randomized, Placebo-Controlled Study to Assess the Safety of Combination Preventive Treatment with Pyridostigmine, DEET, and Permethrin

I. INTRODUCTION

You are being asked to take part in a research study. Before you decide to be a part of this study, you need to understand the risks and benefits so that you can make an informed decision. This is known as *informed consent.*

This consent form provides information about the research study which has been explained to you. Once you understand the study and the tests it requires, you will be asked to sign this form, if you want to take part in this study. ***Your decision to take part is voluntary. This means you are free to choose if you want to take part in this study.***

II. PURPOSE and PROCEDURES

You are being invited to participate in a research study that is designed to determine the safety of pyridostigmine bromide, a medicine intended to prevent death as a result of exposure to a nerve agent. You will not be exposed to nerve agents as part of the study—the study is only intended to assess the safety of pyridostigmine, not how effective it would be in preventing death. In addition, you will have the personal pesticide DEET applied to your skin, and wear military clothing that has been sprayed with another personal pesticide, permethrin. Each of the personal pesticides is widely used throughout the United States, and they are felt to be safe. They are included in this study to assess whether they have any impact on the effects of pyridostigmine. Each of the three treatments will be used exactly as they have been and would be used to protect U.S. military service members deployed to environments posing insect and/or nerve agent threats. In addition to the treatments, you will be asked to march on a treadmill while wearing a backpack, be shown video scenes of war, hear background noises, and solve math problems. These elements have been added to try to mimic a war environment so we can try to see if pyridostigmine has any different effects in a war-like environment than in a restful situation. Although there is considerable evidence that each of the treatments used in the study is safe, there has also been controversy about whether the combination could be related to symptoms in some Gulf War veterans, sometimes called "Gulf War Syndrome" or "Gulf War Illness", which has no clear diagnostic criteria or treatment. Numerous expert scientific panels have found no evidence for a unique illness or syndrome, or for an association between either these treatments or any other exposure in the Gulf War and subsequent illness. However, the Institute of Medicine concluded that "studies are needed to resolve uncertainties about whether PB, DEET, and permethrin have additive effects". That is the purpose of this study.

You will be asked to perform some physical tasks (e.g., manual dexterity, hand-grip, step test, pull-ups) and do some computer-based tests to determine whether the medicine or the stressful environment affects your performance at all. You will also have blood drawn before and after you take medicine or are put in a stress situation, to help us to determine what effects they have on you.

Sixty-four subjects will participate in this research study. Preliminary evaluations will be performed over two days of less than four hours each in an outpatient status. Each subject will then be in the hospital for approximately 30 hours each for four distinct in-patient study periods, each separated by one to two week intervals. ***You may withdraw your consent at any time.*** We reserve the right to remove you from the study at any time at our discretion if circumstances (you don't meet the requirement or consistently do not comply with the procedures) require such actions.

We ask that you be in good general health and have no chronic medical problems. In particular, if you have heart disease, high blood pressure, diabetes mellitus, marked obesity, osteoarthritis, other chronic joint, muscle, or nervous system disorder active, or widespread skin conditions such as eczema, psoriasis or a bad sunburn, you will not be able to participate in the study. If you have a history of allergic reactions to DEET, permethrin, pyridostigmine, or similar compounds you also well not be able to participate. If you take any medications chronically (other than birth control pills), you will not be able to participate. If you are a woman, you must not be pregnant or nursing, or plan to become pregnant during the course of your participation in the study. To avoid becoming pregnant, you should either abstain from sexual relations or practice a method of birth control. Except for surgical removal of the uterus, birth control methods such as the use of condoms, a diaphragm or cervical cap, birth control pills, IUD, or sperm killing products are not totally effective in preventing pregnancy. A pregnancy test will be performed prior to enrollment in the study and prior to each treatment phase (hospital stay).

Before participating in any of the experimental procedures, you will be asked to provide a medical history and undergo a brief physical examination. If the findings of the physical and medical history are normal and show no apparent risk, you will be eligible to participate. Below are brief descriptions of the study procedures and potential risks. We ask that you avoid drinking any alcoholic or caffeine-containing beverages and avoid participating in any strenuous exercise for 24 hours prior to each test session.

III. OVERVIEW OF STUDY AND EXPERIMENTAL PROCEDURES

The study involves taking by mouth a nerve agent pretreatment known as pyridostigmine bromide, or a placebo—a tablet without any expected effects. Pyridostigmine bromide is a chemical compounds known as a carbamate that can effect nerves and muscles. It is approved by the Food and Drug Administration (FDA), and has been safely used for decades in-patients with an autoimmune disease known as myasthenia gravis. Myasthenia gravis is a disease in which someone's own body develops antibodies that block receptors in their muscles, causing muscle weakness that is worsened by physical activity. Pyridostigmine bromide is the treatment of choice for myasthenia gravis, usually starting at a dose of 60 or 120 mg every three or four hours, with an average dose of 600 to 900 mg per day, up to 10 times what will be given in this study. Treatment is life-long for patients with myasthenia, and doses as high as 2,000 to 6,000 mg per day have been used. However, the FDA has not yet approved the use of low doses in healthy subjects in a preventive manner—it is permitted in this research study as an investigational new drug. The dose of pyridostigmine you will take is 30 mg

every 8 hours for four doses on each of two visits. After ingestion you will perform physical and mental tasks.

The table below provides an outline of the entire test schedule. Details of the test sessions and procedures are described.

Description of Study Visits

Visit Number	Pre-Treatment Visits
1	Questionnaire Completion, Blood Draw, Mental Assessment Battery, EKG and Practice Sessions for computerized cognitive test
2	Medical history, Physical Examination and Practice Sessions
3	**Pyridostigmine/DEET/permethrin Visit***
	Rest period*
	Cognitive testing
4	**Pyridostigmine/DEET/permethrin Visit***
	Load Carriage Exercise with Physical and Mental Tasks*
	Cognitive testing
5	**Placebo Visit***
	Rest period*
	Cognitive testing
6	**Placebo Visit***
	Load Carriage Exercise with Physical and Mental Tasks*
	Cognitive testing

*Note: The order of test visits for pyridostigmine and placebo treatments will be randomized, as will the order of visits for rest and exercise/tasks.

A. Questionnaires

You will be asked to complete a medical history form, physical activity questionnaire, and several questionnaires designed to gather information relating to your health, mood, behavior, and hassles or stress in your life. We ask that you answer all items to the best of your ability, but if you are uncomfortable with questions you may choose not to answer them. Each questionnaire will be coded so that your name is not personally identified and your answers are not linked to your name. However, we will keep a list in a locked file which relates your name and code. Thus, the only risk posed by these questionnaires is that of confidentiality, but we will maintain your privacy to the fullest extent provided by the law. All data collected as part of this study will be used for research purposes only and will not be scored or analyzed until the study is completed. You will be asked to provide the name and contact information for your primary doctor, and if you consent we will inform him/her of your participation in this study.

In addition to written questionnaires, the staff may also ask you questions which require short answers; the questions may be asked while you are preparing for the test, during exercise, or during the physical tasks. These questions will pose no risk in that they relate only to the duration of the tasks.

B. Physical Examination and Laboratory Testing

The purpose of this assessment is to try to make sure that you do not have a significant medical problem that could put your health at risk by participation in this study. If you have heart disease, asthma or chronic lung disease, diabetes, severe obesity, kidney or liver disease, or a joint, muscle, or nervous system disorder, you will not be able to take part in the study. On your first visit, blood will be drawn to check your blood counts, kidney function, blood sugar, liver function, and for Hepatitis B as well as HIV. If you are a woman, a pregnancy test will be done. A standard urinalysis will be done. You must read and sign a separate consent form before taking the HIV test. This form can be found on the last page of this document. An electrocardiogram (EKG, or heart tracing) will be obtained. The EKG is obtained by briefly placing a series of electrodes on your chest and arms, which make it possible to record the electrical impulses from your heart on a piece of paper. This tells us whether there is any evidence that you have had a heart attack or other heart disease.

On your second visit, a physician will evaluate the results of your first visit and take your medical history and perform a full (not complete) physical examination (meaning you will not have a rectal, genital or breast exam). You will be informed of any significant abnormalities that are identified. You can expect that each of your first two visits will take about three hours.

C. Hospital Stays

You will be scheduled for four separate stays in the hospital that will each be about 30 hours long, at either the National Naval Medical Center (NNMC), Clinical Pharmacology Unit (Bethesda) or Naval Medical Center San Diego (NMCSD), Naval Health Research Center (NHRC, San Diego). You will be asked to arrive by 0800 (8:00 AM) on the day of admission, and can expect to leave by about 1400 (2:00 PM) the following day. You are responsible for arranging your own transportation to and from the study site. You will be given meals (a standard hospital diet) and a place to sleep. You may bring food with you, though we ask that you do not drink beverages containing alcohol during the time that you are in the hospital. You will need to stay on the hospital grounds for the entirety of each 30-hour period. You will have your vital signs (blood pressure, heart rate, and respiratory rate) checked three times daily.

During each hospital stay, you will be provided with military battle dress uniforms (BDUs, or fatigues) to wear, which have been pre-treated with the insect repellent permethrin or a placebo (a treatment that should have no active effects). You will also be asked to apply a cream to your skin that may or may not contain DEET (the active ingredient in *Off®* and other popular insect repellents). Each of these repellents is widely used and is felt to be safe when used in the manner described. You will also be given a 30 mg pyridostigmine bromide tablet or a placebo (a sugar pill that is not expected to have any active effect) to take by mouth every 8 hours while you are in the hospital. This will mean taking a total of four tablets during each 30-hour period.

You will have a small plastic catheter placed in the vein of one arm during each hospital stay to make it easier to draw blood samples. The catheter will be placed by a

nurse or trained technician. A needle is used to find the vein, then the needle is removed and the catheter is left in the vein, secured to your arm with tape, and a heparin lock is put on the end of the catheter so that you do not need to have another needle stick for each blood sample that is needed. The catheter will be removed after each 30-hour period. The site is cleaned with *Betadyne*® antiseptic and alcohol prior to catheter placement, but there is still a small risk of infection at the site. The study nurse will examine the catheter site regularly, and the catheter will be removed if there are any signs of an infection. A physician will be notified. If an infection develops, it usually resolves with just applying warm compresses; antibiotic treatment is rarely required. You will have about 55 ml (about two ounces) of blood drawn as part of your initial evaluation. During each 30 hour hospital stay you will have 10 ml (two teaspoons) of blood drawn nine times each through the catheter. You will also have about three teaspoons (15 ml) of blood drawn at the end of the study to ensure that your blood counts and kidney and liver function have not changed. The total amount of blood drawn during the entire study is expected to be no more than 430 ml, or about fourteen ounces (for comparison, a blood donation of a pint is about 500 ml.). The blood that is drawn will only be used for the tests described in the study. When you complete your final hospital stay, a physician will perform a brief exit history and physical examination. You will be informed of any significant findings.

If the study physician feels it is medically necessary to stop your participation in the study at any time, you will be told why. If your medical condition warrants hospitalization, you may need to remain at NNMC or NMCSD, or be transferred to another hospital until your medical condition returns to an acceptable level.

Please inform the study physician of any prescription or over-the-counter medications you take. You are asked to refrain from taking any medication during your hospital stays. Please do not take any medication other than birth control pills or simple pain relievers (acetaminophen or ibuprofen) or cold medicines for at least one week before starting the study.

D. Potential Risks of Treatments

Procedure	Potential Risk	Likelihood of Risk	Severity of Risk
Ingestion of Pyrido-stigmine bromide (PB)	Slowed heart rate (by about 5 beats per minute)	Common	No health risk
	Slight increase in flatus (gas) and occasional looseness of bowels (diarrhea)	Common	Not serious
	Rash	Rare	Not serious
	Airway tightening or reactivity	Can occur in those at risk for asthma	Usually mild, can be moderately serious

	Birth defects if taken by pregnant women	Crosses the placenta, but no risk seen with much higher doses in animal studies, and in pregnant women with myasthenia gravis. Classified by the FDA as a drug in which risk can not yet be excluded. May cause risks to subject, fetus, or embryo that are as yet unforeseen.	Serious
	Questionable association with symptoms such as depressed mood, headaches, fatigue, memory problems, muscle and joint pain that have been described by some as "Gulf War Syndrome"	Studies show such symptoms are not seen more commonly with PB than placebo, and there has been no association between Gulf War veterans' reports of taking PB and any particular symptoms	Ranges from not serious to serious depending on the of number and type of symptoms
Application of DEET to skin	Rash	Relatively uncommon unless rash already present	Not serious
	anaphylaxis, seizures or encephalopathy	Extremely unlikely—seen only in children with excessive, inappropriate use	Very serious

Wearing of uniform with permethrin	Rash	Uncommon when directly applied to skin; unlikely with application only to uniform	Not serious
Placement of heplock in vein in arm and drawing of blood	Infection	Uncommon due to antiseptic technique, close monitoring, and short duration of placement	Usually not serious, treated by removing catheter and applying warm soaks; sometimes requires antibiotics
Treadmill march & physical performance tasks	Muscle fatigue and soreness	Likely	Not serious
	chest pain or cardiac symptoms in subjects with undetected heart disease	Unlikely due to initial selection and screening process	Serious
View videotapes of war scenes	Fear, nightmares	Unlikely since tapes are made mostly from popular movies	Not serious

DEET and permethrin are widely available. If you have ever had side effects with Off® or other insect repellents that may have included DEET, you should notify the investigators. If you have ever had an allergic reaction to permethrin (Nix®, commonly used to treat head lice) other pyrethrin compounds that sometimes are used in household pesticides, or the flowers chrysanthemums (mums), please notify the investigators. Permethrin has *not* been studied in pregnant women, but it has *not* been shown to cause birth defects or other problems in animal studies. Finally, if you have had problems with anesthesia in the past, such as taking a long time to recover from anesthesia, please notify the investigators, as this might place you at a slightly higher risk of side effects from the pyridostigmine bromide.

During the Persian Gulf War, pyridostigmine bromide was used by American and British troops at the same dose you will take to try to provide protection in case troops were exposed to lethal nerve agents. Although the opposing Iraqi Army developed nerve agents, fortunately they did not use them during the war. More than 200,000 service members took pyridostigmine for one to four days during the ground war with Iraq. American soldiers also were provided with DEET, with two or three cans given out for every soldier deployed. However, insects were a primarily a problem early in the deployment, long before pyridostigmine was used, so it is unlikely that many soldiers used DEET while they were taking pyridostigmine. Permethrin was also

available for application to uniforms, and it is estimated that 2% (one out of 50) of American soldiers used this. Since the Gulf War, some veterans have reported a variety of ill-defined symptoms (fatigue, difficulty concentrating or remembering things, muscle and joint aches), and some have suggested that pyridostigmine, immunizations, or other treatments or exposures could have a role in causing their symptoms. Some researchers have since found that extremely high doses of pyridostigmine, DEET, and permethrin (estimated at more than 10,000 times the maximum to which soldiers were exposed) were harmful to chickens. Chickens and other types of birds are also more susceptible to cholinesterases (such as pyridostigmine). Although it is difficult to apply their results to humans, it does indicate a need to study the combination carefully in humans. Examination of tens of thousands of Gulf War veterans in the Comprehensive Clinical Evaluation Program has not identified any relationship between their use of pyridostigmine, and/or pesticides such as DEET or permethrin, and any symptoms or diagnoses. Your investigators can discuss this further and provide additional information to you if you wish.

E. Physical and Mental Tasks

1. You will exercise by walking on the treadmill for one hour carrying a pack weighted to equal 30% of your body weight (up to a maximum pack weight of 72 pounds). The grade of the treadmill will be 5% and the speed will be 3.5 mph. A physician will be present throughout your marching on the treadmill. Please notify the physician if you begin to experience any chest pain or discomfort, or difficulty breathing, during the test. **Please note that you may terminate the exercise at anytime.**

2. While you are walking on the treadmill, you will be shown videotapes of war scenes, with occasional loud noises in the background. In addition, you will be asked to solve increasingly complex mathematical problems (e.g., adding and subtracting sums). These tasks and environmental factors are intended to simulate a war environment. Segments of the videotapes may contain graphic or disturbing footage of war scenes.

3. **Physical Performance Tasks:** You will complete a series of tests to measure certain physical abilities: manual dexterity, handgrip strength, and lower and upper body strength. These tests are part of a performance test battery developed by the Naval Medical Research Center. You will complete these tasks after the load carriage tests. Following are brief descriptions of the tasks.

a. Manual Dexterity

You will disassemble and reassemble a weapon as quickly as possible to evaluate the motor skills of your hands and fingers. Once you begin to disassemble the weapon, an investigator will begin timing you with a stopwatch. When you complete the reassembly and place the weapon down on the table in front of you, the investigator will end the timing period. This task poses no risk to you.

b. Hand-Grip Test

Using a device which you hold in your hand and squeeze, your maximal grip will be tested. After a brief rest, you will compress the dynamometer to a force equal to 30% of your maximal grip and maintain this compression as long as possible. You may experience muscle pain and tiredness in your hand, but this will only last a short time.

c. Lower Body Strength

You will be instructed to perform a step test on two 10-inch steps: you must complete as many steps as possible within 60 seconds while wearing a 20 kg waist belt. The task begins when the investigator says "READY, GO". You must mount and dismount while placing your alternate foot on each step. After 60 seconds the investigator will say "STOP". At the end of this test you may experience muscle fatigue and soreness in the exercising muscles--the type of discomfort common with any form of strenuous exercise. These are only temporary sensations and should disappear within several minutes. Spotters will stand on each side and in the back of the steps to prevent any injury.

d. Upper Body Strength

You will grasp the pull-up bar with your palms facing forward and touch your chin on the horizontal bar at the height of each pull-up. Once you have completed as many pull-ups as possible, you will release your grip. At the end of this test you may experience muscle fatigue and soreness in the exercising muscles--the type of discomfort common with any form of strenuous exercise. These are temporary sensations and should disappear within several minutes. In addition, it is possible for you to lose your grip and slip from the bar. In order to prevent any injury, spotters will stand on each side of the pull-up bar. These spotters can also help you descend the short distance to the ground once you complete your pull-ups.

4. Mental Tasks

Prior to the experimental tasks, you will complete a mental assessment battery which will take less than two hours. The battery will include tasks related to memory, arithmetic, reaction time, reasoning, recall, and hand dominance. It poses no risk to you. In addition, before and after the load carriage task you will complete a computer test which evaluates several areas of mental function. The tasks will include code substitution, a memory task, mathematical processing, and visual, spatial and auditory monitoring. These are the tasks you will have practiced on at least six occasions before being scheduled for the load carriage condition. For this assessment one task will be presented at a time first, and then, four tasks which occur simultaneously will be presented. You will begin the task and continue for a period of no more than 30 minutes. You must respond quickly and accurately to each task in order to accumulate points; your performance is evaluated by the number of points accumulated at the end of the task. To our knowledge, there are no risks associated with this test, but you may experience some degree of anxiety. You will be given instructions on the details of the test, shown the computer screen and appropriate controls, and as stated above, undergo at least six practice sessions prior to undergoing the actual test.

IV. TO BE INCLUDED IN THIS STUDY:

1. You must be between 18 and 49 years old.
2. You must read, understand and sign this consent form.
3. You must comply with study requirements and follow the CPU/NHRC rules provided to you.
4. You must not test positive for hepatitis B, or HIV-1 (the virus that causes AIDS).
5. You must not have a history of any significant medical disease.
6. You must not be pregnant.
7. You must be within 20% of your ideal body weight.
8. You must have no clinically significant medical or psychiatric illness.
9. You must not have any clinically significant abnormalities on blood tests or EKG.
10. You must be eligible for medical care in the Department of Defense healthcare system—either an active duty service member, retired from active duty, or a dependent of an active or retired service member.
11. You must meet all entry criteria in order to participate in this study.

V. POTENTIAL BENEFITS TO YOU

The study is designed for research purposes and not intended to be of direct benefit to you.

VI. PAYMENT FOR PARTICIPATION

Subjects will be paid for participation in each study. If you complete the entire study you will be paid $950. In addition, your meals and lodging at the hospital will be paid for. Payments will be made after completing the study. If you withdraw before the end of the study, you will be paid only for tests that you completed. If either your participation, or the overall study, is stopped unexpectedly because of evidence of apparent harm resulting from participation, you will be paid only for tests that you completed. Payment for dependents and retirees will be according to the following schedule:

Study Days	
- Two 4-hour outpatient days	$80.00
- Four 30-hour inpatient stays	$360.00
Lab Tests	$100.00
Pharmacokinetics	$90.00
Electrocardiograms	$20.00
Medication Administration	$300.00
TOTAL	$950.00

Active duty service members will be paid only according to the number of blood draws obtained. It is expected that a total of thirty-eight blood draws will be required (nearly all facilitated through the use of a heparin lock which will be put in place for each inpatient stay). Payment for active duty service members will therefore be $25 per blood draw, for a total payment of $950 upon completing the entire study.

VII. RIGHT TO WITHDRAW

Participation in this study is voluntary. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. You may discontinue your participation at any time without penalty or loss of benefits. You should let the study leader know if you decide to stop taking part in the study. We also reserve the right to remove you from the study at any time at our discretion if circumstances (such as failure to follow instructions) require such actions.

VIII. RECOURSE IN THE EVENT OF INJURY

Should you be injured as a direct result of participating in this research project, you will be provided medical care, at no cost to you, for that injury. You will not receive any injury compensation, only medical care. You should also understand that this is not a waiver or release of your legal rights. You should discuss this issue thoroughly with the principal investigator before you enroll in this study.

In the event of a medical emergency while participating in this study, you will receive emergency treatment in the facility you are in or a nearby Department of Defense (military) medical facility (hospital or clinic). You will be provided with any and all medical care that you need at no expense to yourself.

If you believe the government or one of the government's employees (such as a military doctor) has injured you, a claim for damages (money) against the federal government (including the military) may be filed under the Federal Torts Claims Act. If you would like to file a claim please contact the University's Office of General Counsel and request the filing forms.

If at any time you believe you have suffered an injury or illness as a result of participating in this research project, you should contact the Office of Research at the Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814 at (301) 295-3303. This office can review the matter with you, provide information about your rights as a subject, and may be able to identify resources available to you. Information about judicial avenues of compensation is available from the University's General Counsel at (301) 295-3028.

IX. PRIVACY AND CONFIDENTIALITY

The Institutional Review Board/Committee for the Protection of Human Subjects of Uniformed Services University of the Health Sciences and Naval Health Research Center may review your study records as part of their duties to protect research participants. Officials from the Food and Drug Administration, the United States Army Medical Research and Materiel Command, the Office of Naval Research and the Surgeon General's Human Subjects Research Review Board may also view these data as part of their responsibility to protect human subjects in research. A study monitor (doctor) has

been appointed at each site to review possible side effects that may occur, and the monitor may need to review your medical records in the course of their evaluation. A Data Safety Management Board of three doctors will review the results of the study at three-month intervals, and will have access to study records in order to ensure that you are not being harmed unnecessarily by participation in this study. Except for those people, records from this study will be kept private unless law requires disclosure. No reports from this study will use your name or identify you personally.

All information that you provide as a part of this study will be confidential and will be protected to the fullest extent provided by law. Information that you provide and other records related to this study will be kept private, accessible only to those persons directly involved in conducting this study and to those individuals who provide oversight for human subjects protection. All questionnaires and forms will be kept in a restricted access, locked cabinet while not in use. However, please be advised that under UCMJ, a military member's confidentiality cannot be strictly guaranteed. To enhance your privacy of the answers that you provide, data from questionnaires will be entered into a database in which individual responses are not identified. After verification of the database information, the hard copy of the questionnaires containing identifiers will be shredded.

It is the policy of the U.S. Army Medical Research and Materiel Command that data sheets are to be completed on all volunteers participating in research for entry into this Command's Volunteer Registry Data Base. The information to be entered into this confidential data base includes your name, address, Social Security number, study name and dates. The intent of the data base is two-fold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years.

****IF YOU HAVE ANY QUESTIONS PLEASE FEEL FREE TO ASK THEM****

I have read the explanation of this study on this form. The test procedures have been reviewed and all my questions have been answered. I understand the nature of the study and I volunteer to participate in it. I attest that I meet the requirements for participation in this study. I understand that the study is designed for research purposes and not to be of direct benefit to me.

If you have any additional questions, you should contact Dr. Michael Roy of USUHS, Bethesda, Maryland 20814 at (301) 295-3617. He has agreed to discuss the study and the results of your tests with you. In the San Diego area, you may contact Dr. Paul Sato of the Naval Health Research Center, at (619) 524-0069, who has also agreed to discuss the study and your results with you. If you have questions about your rights as a research subject, you should call the Director of Research Programs in the Office of Research at USUHS (301-295-3303). This person is your representative and has no connection to the investigators conducting the studies.

The investigator will inform you of any significant new findings that develop during the course of the research that could influence your willingness to continue your participation in the study.

By signing this informed consent, I am agreeing that the study has been explained to me and that I understand the study. I am signing that I agree to take part in this study but I may withdraw my consent to participate at any time without prejudice to future contacts with the USUHS. I will be provided a copy of this consent form.

I AGREE TO PARTICIPATE IN THE FOLLOWING PROCEDURES:

NOTIFICATION OF MY DOCTOR OF PARTICIPATION IN THIS STUDY

QUESTIONNAIRES	LOAD CARRIAGE ENDURANCE
EXERCISE	
URINE COLLECTIONS	BLOOD DRAWS
MANUAL DEXTERITY	HAND-GRIP STRENGTH
STAIR STEPPING	PULL-UPS
MENTAL TASKS	WEAR BATTLE DRESS UNIFORMS
APPLY DEET TO SKIN	INGEST PYRIDOSTIGMINE BROMIDE

NAME: _____

SIGNATURE: _____ **DATE:**_____

ADDRESS: _____

WITNESS NAME: _____

SIGNATURE: _____ **DATE:**_____

I certify that the research study has been explained to the above individual, by me or by my research staff, and that the individual understands the nature and purpose, the possible risks and benefits associated with taking part in this research study. Any questions that have been raised have been answered.

INVESTIGATOR: _____ **DATE:** _____

HIV ANTIBODY TEST INFORMED CONSENT

General Information I have discussed the test for the antibody to Human Immunodeficiency Virus (HIV), the virus that causes Acquired Immunodeficiency Syndrome (AIDS), with my health care provider. HIV can be transmitted from HIV infected persons to others through sexual contact (heterosexual and homosexual), HIV-infected blood transfusions, sharing needles with others (as can occur with drug abuse), and from HIV-infected mothers passing HIV-infection to their unborn child.

Need For Test I understand that this HIV blood antibody test has been recommended for me because my doctors could use the information obtained to better deliver health care. If I do not have the test, I understand that my health care providers will have less information with which to counsel me about my health, or about the risks of passing the virus to my sex or needle-sharing partner(s). If I am pregnant and infected with HIV, I can transmit the infection to my baby during pregnancy or at delivery and my baby may then become sick and die. I understand that the doctor needs to test me so that he/she can have better information to take better care of my health and my baby's health.

Test I understand that the test can only tell if I am infected with HIV. A positive test does not mean that I have AIDS and the test cannot tell me definitely if I will become ill. This determination usually requires additional evaluation and testing. The HIV blood antibody test involves withdrawing a sample of my blood (approximately 5-10 cc or 1-2 tsp.). One or more laboratory tests will be done to see if HIV antibodies are present in my blood, and part of the blood sample may be frozen and stored for further testing. Although HIV blood antibody tests are both highly accurate and precise, occasionally incorrect and confusing results can be reported that cause anxiety for patients. In rare cases, it is possible that HIV blood antibody testing can fail to detect the presence of HIV infection, especially when persons have recently been infected with HIV. If questionable or confusing results are reported by this test, I may be requested to consent to submit to a second blood test to clarify the situation. Sometimes as long as several weeks can elapse before the results of HIV blood antibody tests can be available.

Test Results Every attempt will be made to keep the results of my HIV blood antibody test confidential within applicable laws and regulations; however, confidentiality cannot be absolutely guaranteed. I understand that a positive HIV blood antibody test can have a negative impact on my personal relationships, my job, my health, and/or my life insurance. In particular, active duty service members should be aware of requirements to report positive HIV test results to military authorities. I should arrange an appointment with my doctor for a later date in order to be counseled about the results and meaning of my HIV blood antibody test. The results will be documented in my medical record at that time. If my testing is positive, I understand that it is my responsibility to tell my sex partner(s) and anyone with whom I share or have shared needles that I am HIV-infected. If I do not want to tell my sex or needle-sharing partners, I understand that the Maryland Public Health Department may be obligated to tell them.

Alternatives & Consent My decision not to have HIV blood antibody testing will not result in the denial of benefits or health care to which I am entitled under applicable regulations. I am aware that anonymous HIV blood antibody testing is available through Public Health Clinics in my state of residence. I acknowledge that I have been given the opportunity to ask questions and discuss my concerns regarding the HIV blood antibody test, and all such questions have been answered by my health care provider to my satisfaction. By my signature below, I acknowledge that I have given my consent for the performance of the HIV antibody test for my blood.

Patient's Signature/Printed Name	Date Signed
Witness Signature/Printed Name	Date Signed

UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
F. EDWARD HEBERT SCHOOL OF MEDICINE
4301 JONES BRIDGE ROAD
BETHESDA, MARYLAND 20814-4799

June 19, 2000

MEMORANDUM FOR MAJ(P) MICHAEL J. ROY, M.D., DEPARTMENT OF

MEDICINE SUBJECT: Approval of Protocol G183LZ for Human Subject Use

Your research protocol entitled ***"Randomized, Placebo-Controlled Study to Assess the Safety of Combination Preventive Treatment with Pyridostigmine, DEET, and Permethrin,"*** was given **full review** by the USUHS Institutional Review Board (IRB) on 15 June 2000 and was **approved for execution** pending revisions to the consent form stipulated by the IRB. These revisions have been received and have been reviewed and approved. The consent form approved for use is attached. **Please use photocopies of the stamped and approved informed consent document when obtaining consent from subjects being enrolled.** ***The original stamped and approved consent form should be maintained in your files.*** It is your responsibility to maintain an accurate and accessible file of all consent forms of participating human subjects.

If collection and/or analysis of data for your study is to continue beyond one year, the IRB must perform a continuous (annual) review and provide written approval. Federal oversight agencies have found this to be a frequent source of problems during their audits, and have stated clearly that studies that have not received at least annual approval by the IRB of record must terminate activity immediately since they are no longer in compliance. In order for ongoing human subject research studies to be reviewed, approved and processed by the IRB within this time constraint, a status report (USUHS Form 3204A) must be received by the IRB office within 90 days of the IRB approval anniversary. Though we will attempt to assist you by sending you a reminder, this reporting requirement is your responsibility.

Please notify this office of all amendments/modifications to this protocol and provide us with copies of any amendment/modification approvals from the appropriate human use committees overseeing this study (i.e., NHRC, etc.). This office should also be notified of any untoward events that occur in the conduct of this project. If you have any questions regarding human subject research, please do not hesitate to call me at 301-295-3303.cc: Director, Research Administration

'Richard R. Levine,
LTC, MS, USA
Director, Research Programs and
Executive Secretary, IRB

UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
F. EDWARD HEBERT SCHOOL OF MEDICINE
4301 JONES BRIDGE ROAD
BETHESDA, MARYLAND 20814-4799

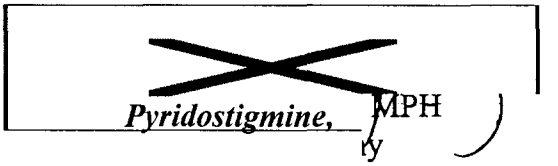
September 17, 2003

MEMORANDUM FOR INSTITUTIONAL REVIEW BOARD, USUHS

SUBJECT: Approval for request to analyze data, Protocol G183LZ

Based on my communication with LT John R. Ashburn Jr. (083-68-4646), USN, Department of Medical and Clinical Psychology USUHS, I would like to extend my approval for his request to analyze data collected in conjunction with the following study:

"Randomized, Placebo-Controlled Study to Assess the Safety of Combination Preventive Treatment with DEET, and Permethrin"



If you have any questions or concerns regarding this approval please feel free to contact me.

Michael J. Roy, MD
LTC, MC, U.S.
Director, Division of Military Internal Medicine
Associate Professor of Medicine
USUHS
PH: (301) 295-9601
e-mail: mroy@usuhs.mil

Appendix C

L-Tyrosine methodology, IRB approval, and permission to use data

METHODS

Subjects

The study was approved by the Institutional Review Board of the Uniformed Services University of the Health Sciences and a written consent was obtained from all subjects prior to participation. Subjects were carefully screened (medical history, physical exam) by a physician prior to any procedures. Twenty healthy, moderately to highly physically fit males participated in the study; all refrained from prescription medications and vitamin-mineral supplements and all were non-smokers. Exclusion criteria included medical diagnosis with diabetes, chronic fatigue syndrome, or fibromyalgia, any history of clinical depression, thyroid and other endocrine diseases, bulimia or anorexia, hypertension, cardiac disease, liver disease, obesity, and use of chronic medications or nutritional supplements.

Design

The study was a double-blind, placebo-controlled, crossover design. Subjects underwent a maximal exercise treadmill test to determine maximal oxygen uptake (VO_2Max). After which, they performed practice sessions to attain proficiency on physical and cognitive performance test batteries: 1) a 1mg dexamethasone suppression classification test, 2) a tyrosine load carriage exercise test preceded by the cognitive performance battery and followed by the physical and cognitive performance test batteries, and 3) a placebo tyrosine load carriage exercise test preceded by the cognitive performance battery and followed by the physical and cognitive performance test batteries. All testing was conducted in the Human Performance Laboratory (HPL), USUHS in the morning on three separate days, each test separated by at least one week to allow for physical recovery. The tyrosine and placebo conditions were randomly assigned, and neither subject nor tester were aware of the test condition.

Exercise Testing

The maximal exercise test was conducted on a motorized treadmill (Quinton Medtrack ST65, Quinton Instruments, Bothell, WA). Thirty minutes prior to beginning the test, a peripheral catheter was inserted in the antecubital fossa of a forearm for blood sampling; the catheter was kept patent with a heparin lock. The test began with a 5-minute walk at 3.0 mph and 2% grade, after which; the speed was increased to between 5.0 and 8 mph, depending on the subjects' heart rate at the end of the warm-up, the grade was set to 0% incline. The grade was then increased by 2.5% increments every three minutes. Prior to each grade change, a blood sample was collected for lactic acid analysis; exercise continued until volitional exhaustion (Kyle). Oxygen uptake and CO_2 production during all exercise tests was determined either a Metabolic Measurement Cart 2900c (SensorMedics, Yorba Linda, CA) or the K4b^2 (CosMed, Rome, Italy).

In the classification test, an intravenous catheter was inserted in the subject sixty minutes prior to the start of the test. The exercise began with a 5-minute warm-up at 50% VO_2 Max at a 5% grade. Next, the exercise intensity was increased for 10 minutes to 70% VO_2 Max at a 10% grade, followed by five minutes at 90% VO_2 Max at a 10% grade. The subjects cooled down at 3 mph and a 2% grade for five minutes. Following the completion of the treadmill work, the subject participated in the physical and then cognitive performance batteries.

The load carriage exercise required that the subject wear a backpack weighted to 30% of his body weight (up to a maximum pack weight of 72 pounds). The subject began with a 5-minute warm-up at 50% VO_2 Max at a 3% grade. Following the warm-up, the grade was increased to 5% and the speed was adjusted to achieve 70% of the subject's VO_2 Max; this speed (3.7 mph $\pm$ .02) and the grade was maintained for the entire 120 minutes or until volitional exhaustion. Upon exhaustion, the backpack was removed, and the subject walked at 3.5mph at a 2.5% grade for five minutes. Perceived exertion was measured by the Borg scale (Borg). Metabolic data, heart rate, blood samples and subject responses to Subjective Exercise Experience Scales (SEES) were obtained before, during and after exercise (McAuley). The physical and cognitive performance batteries immediately followed the load carriage test.

Physical Performance Battery

Subjects underwent practice sessions in order to attain proficiency on a physical performance battery designed to measure manual dexterity, handgrip strength, lower body strength and coordination and upper body strength and endurance. The specific physical tasks included: 1) a timed session for disassembly and reassembly of a military weapon; 2) a maximal voluntary contraction (MVC) with a handgrip dynamometer followed by an isometric contraction equivalent to 30% of the MVC for as long as possible; 3) the maximum number of stairs stepped in one minute while wearing a 20kg weight belt; and 4) as many pull-ups as possible. This group of tests was a subset of a performance test battery developed by The Naval Medical Research Institute (NMRI), Bethesda, MD (Hyde).

Cognitive Performance Battery

Two cognitive performance assessment batteries were used. Synwork1 developed by The Activity Research Services, San Diego, CA and NASA Space flight Cognitive Assessment Tool (S-CAT), Version 2.2. The S-CAT is a neuropsychological test used to assess on-orbit cognitive status during flight missions. While the Synwork1 is designed to assess performance in a simulated work environment by using four task-designated quadrants for measuring working memory, arithmetic, visual monitoring simultaneously.

Subjects were required to achieve stable scores on the cognitive performance batteries prior to participating in the two load sessions. Following an initial battery demonstration, the subject underwent six supervised practice sessions until a baseline was noted. The results of each session were stored and progress was monitored by one of the researchers. The cognitive performance batteries were administered following completion of the physical performance battery on each of the two load sessions. It took the subjects approximately 30 minutes to complete two batteries.

Ingestion of Tyrosine or Placebo

Tyrosine (150 mg/kg l-crystalline tyrosine in 70g of applesauce) and placebo (7g microcrystalline cellulose in applesauce) were prepared and coded by a local pharmacy (Pathways, Bethesda, MD). The pharmacist kept the code until data collection was completed in order to maintain double-blinded status of the study. In the HPL, the tyrosine or placebo mixture was prepared by mixing the set volume of applesauce with the coded supplement. The mass of the supplement added, 150 mg/kg for tyrosine and 7

grams for the placebo, was calculated based on the subject's weight on the date of their VO_2 Max.

Subjects were hydrated sixty minutes prior to testing, and thirty minutes prior to each load carriage session. Subjects were also hydrated with 200 ml of fluid during the load and immediately upon completion.

Dietary Control

A list of tyrosine-dense foods was provided to the subjects, and they were asked to avoid 24-hours prior to testing. The list included bananas, meats, pickled foods, cheeses (with the exception of cottage and cream chesses), chocolate, any whole wheat products, and dairy products. In addition, subjects were asked to refrain from consumption of caffeine and alcoholic beverages for 24-hours prior to testing. Subjects were encouraged to eat carbohydrate dense foods such as bagels, potatoes and white pasta with red sauce the night before testing. All subjects were required to record their dietary intake on the day preceding the first load carriage test and were asked to duplicate the intake for the second test. Subjects were requested to refrain from eating or drinking after 10:00pm the night before the load tests.

Biochemical Assays

Blood samples during the VO_2 Max (1.5ml) for measuring lactate and glucose were collected in heparinized test tubes containing sodium fluoride; samples were centrifuged and the plasma was kept refrigerated at 8-10 °C until assayed within 24-hours (YSI Analyzer, Model 2700, Yellow Springs Instrument Co., Inc, Yellow Springs, OH). Blood draws for the load carriage test sessions were taken at time points –35, +60, Post-exercise, Post pull-up, and Post cognitive. Plasma samples for cortisol and ACTH were collected in chilled EDTA tubes, centrifuged and store at -80°C until analysis by radioimmunoassay (Diagnostics Products Corporation, Los Angeles, CA). Blood for measuring tyrosine (1.oml) was collected in chilled sodium heparin tubes, centrifuged and the plasma was stored at -80°C. Plasma tyrosine concentrations were measured by high performance liquid chromatography (HPLC) (Massachusetts Institute of Technology, Clinical Research Center, Cambridge, MA). Whole blood (1.0ml) was collected in EDTA tubes for measuring hemoglobin and hematocrit by Baker Cell Counter (System 9000, ABX Diagnostic, Irvine, CA).

Statistical Analysis

The Statistical Analysis System (SAS Institute Inc, Cary, NC) computer package was used for all statistics. Data are presented as mean $\pm$ SEM. The data were analyzed as a two-way repeated measure Analysis of Variance. The level of significance was set at $p < 0.05$.

UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
4301 JONES BRIDGE ROAD
BETHESDA, MARYLAND 20814-4799

December 15, 1998

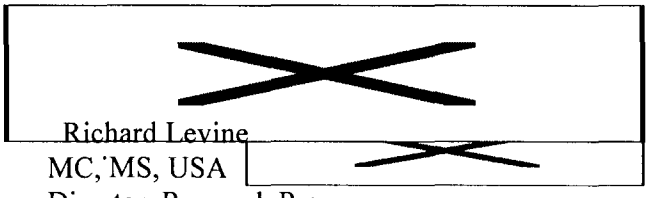
MEMORANDUM FOR PATRICIA A.DEUSTER, PH.D., M.P.H., DEPARTMENT OF MILITARY AND EMERGENCY MEDICINE

SUBJECT: IRB Approval of Protocol **G19190** for Human Subject Research

Your research protocol entitled ***"Tyrosine Effects on Performance"*** was given **full review** by the USUHS Institutional Review Board (IRB) on 10 December 1998 and was **approved** for execution pending revisions to the consent form stipulated by the IRB. These revisions have been received and have been reviewed and approved. The consent form approved for use is attached. Please use photocopies of the stamped and approved informed consent document when obtaining consent from subjects being enrolled. It is your responsibility to maintain an accurate and accessible file of all consent forms of participating human subjects.

The purpose of this randomized, double-blind study is to investigate whether taking tyrosine affects physical and mental performance. The IRB understands that after baseline testing, 16 subjects will undergo a variety of physical exercise and mental tests after a one-time dose of either Tyrosine or a placebo.

If collection and/or analysis of data for your study is to continue beyond one year, the IRB must perform a continuous (annual) review and provide written approval. Federal oversight agencies have found this to be a frequent source of problems during their audits, and have stated clearly that studies that have not received at least annual approval by the IRB of record must terminate activity immediately since they are no longer in compliance. **In order for ongoing human subject research studies to be reviewed, approved and processed by the IRB within this time constraint, a status report (USUHS Form 3204A) must be received by the IRB office within 90 days of the IRB approval anniversary. Though we will attempt to assist you by sending you a reminder, this reporting requirement is your responsibility.**



Richard Levine
MC, MS, USA
Director, Research Programs
and Executive Secretary, IRB

Please notify this office of any amendments you wish to propose and of any untoward events that occur in the conduct of this project. If you have any questions regarding human subject research, please do not hesitate to call me at 301-295-3303.

UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
--4301 JONES BRIDGE ROAD BETHESDA, MARYLAND 20814-4799

Department of Military and
Emergency Medicine Applied
Human Biology Division
Phone: (301) 29 20
DSN: 295-3020
FAX: (301) 295-1645

September 23, 2003

MEMORANDUM FOR INSTITUTIONAL REVIEW

BOARD, USUHS SUBJECT: Approval for Request to

Analyze Data, Protocol **G29190**

Based on my communication with LT John R. Ashburn Jr. (083-68-4646), USN, Department of Medical and Clinical Psychology USUHS, I would like to extend my approval for his request to analyze data collected in conjunction with the following study:

"Tyrosine Effects on Physical and Cognitive Performance"

If you have any questions or concerns regarding this approval please feel free to contact me.

Patricia A. Deuster,
Ph.D., M.P.H.
Professor and Director,
e-mail:
pdeuster@usuhs

Appendix D

Informed Consent Document for Participation in Study 2

Title of Project: Confirmatory Analysis of Selected Computerized Measures: Divergent and Convergent Validity

Principal Investigator: John R. Ashburn Jr.

I. INTRODUCTION

You are being asked to take part in a research study. Before you decide to be a part of this study, you need to understand the risks and benefits so that you can make an informed decision. This is known as *informed consent.*

This consent form provides information about the research study that has been explained to you. Once you understand the study and the tests it requires, you will be asked to sign this form, if you want to take part in this study. ***Your decision to take part is voluntary. This means you are free to choose if you want to take part in this study.***

II. PURPOSE and PROCEDURES

You are being invited to participate in a research study that is designed to determine the validity of a brief computerized performance assessment battery as an index of cognitive strengths and weaknesses.

You will be asked to complete paper and pencil and computer-based behavioral tasks that are indexes of neuropsychological functioning to determine whether the computer-based tasks provide similar or unique information in comparison with the paper and pencil tasks.

80 subjects will participate in this research study. Each evaluation will be performed over a single two-hour period of time. ***You may withdraw your consent at any time.*** We reserve the right to remove you from the study at any time at our discretion if circumstances (you don't meet the requirement or consistently do not comply with the procedures) require such actions.

We ask that you be in good general health and have no chronic medical problems. In particular if you have a nervous system disorder, any neurological condition, current psychiatric condition requiring treatment, or have ever had a head injury with a loss of consciousness, you will not be able to participate in the study.

III. OVERVIEW OF STUDY PROCEDURES

The study involves completing paper-and-pencil and computerized behavioral tasks over a two-hour block of time. You will be asked to complete a brief history form that will be based on questions asked of you by the examiner. The purpose of this history questionnaire is to determine whether or not there are any past medical or developmental factors that could impact your performance on the study tasks. The paper-and-pencil

tasks will include neurocognitive measures of general word knowledge, attention, visuomotor tracking, learning and memory, reasoning, and fine motor dexterity. These tasks pose no risk to you. In addition, you will complete a series of five computer-based behavioral tasks that evaluate several areas of cognitive functioning. These tasks are designed to measure information processing efficiency associated with reaction time, attention and concentration/working memory, learning and memory, spatial perception, and speeded arithmetic calculation abilities. You will take these computer-based tasks immediately before completing the paper-and-pencil tasks. You must respond quickly and accurately to each of the computer-based tasks in order to achieve the strongest scores.

IV. POTENTIAL RISKS FOR PARTICIATING IN THIS STUDY

To our knowledge, there are no risks associated with completing the computer-based tasks. In some instances, individuals may be slightly uncomfortable working with basic thinking tasks that can be intellectually challenging. While most people tend to find these tasks interesting and a little bit fun, occasionally some individuals become anxious about concerns that they may not be doing very well. In the event that you experience such concerns, please inform the study representative so that we can help you to understand the purpose of the testing for research use. You will be given instructions for completing each task, will be shown the computer screen and appropriate controls, and will have an examiner present with you while completing both the computer-based and paper-and-pencil tasks.

The tasks administered in this study are for research purposes only and will not be used for clinical outcome purposes. However, if any obvious difficulties with your thinking are seen during this study, you will be referred to see a licensed psychologist (Dr. Wendy Law) who will discuss the concerns with you and help you to obtain professional assistance and referral.

V. TO BE INCLUDED IN THIS STUDY:

12. You must be at least 18 years old.
13. You must read, understand and sign this consent form.
14. You must comply with study requirements.
15. You must have no clinically significant medical or psychiatric illness.
16. You must meet all entry criteria in order to participate in this study.

VI. POTENTIAL BENEFITS TO YOU

The study is designed for research purposes and not intended to be of direct benefit to you.

VII. PAYMENT FOR PARTICIPATION

Nonmilitary subjects will be paid $30.00 for complete participation in the study. If you are active duty military, you cannot be paid for participating in this research study, in accord with DoD policy.

VIII. RIGHT TO WITHDRAW

Participation in this study is voluntary. You may discontinue your participation at any time without penalty. You should let the examiner know if you decide to stop taking part in the study.

IX. RECOURSE IN THE EVENT OF INJURY

There are no direct risks to you for participating in this study. In the event of a medical emergency while participating in this study, you may receive emergency treatment in the facility you are in or a nearby Department of Defense (military) medical facility (hospital or clinic). Treatment/care will be provided even if you are not eligible to receive such care. Care will be continued until the medical doctor treating you decides that you are out of immediate danger. If you are not entitled to care in a military facility, you may be transferred to a private civilian hospital. The attending doctor or member of the hospital staff will go over the transfer decision with you before it happens. The military will bill your health insurance for health care you receive which is not part of the study. You will not be personally billed and you WILL NOT be expected to pay for medical care at our hospitals. If you are required to pay a deductible you may make a claim for reimbursement through the Uniformed Services University Office of General Counsel.

In case you need additional care following discharge from the military hospital or clinic, a military health care professional will decide whether your need for care is directly related to being in the study. If your need for care is related to the study, the military may offer you limited health care at its medical facilities. This additional care is not automatic.

If at any time you believe you have suffered an injury or illness as a result of participating in this research project, you should contact the Office of Research at the Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814-4799 at (301) 295-3303. This office can review the matter with you, can provide information about your rights as a subject, and may be able to identify resources available to you. If you believe the government or one of the government's employees (such as a military doctor) has injured you, a claim for damages (money) against the federal government (including the military) may be filed under the Federal Torts Claims Act. Information about judicial avenues of compensation is available from the University's General Counsel at (301) 295-3028.

X. PRIVACY AND CONFIDENTIALITY

The Institutional Review Board/Committee for the Protection of Human Subjects of Uniformed Services University of the Health Sciences may review your study records as part of their duties to protect research participants. Except for those people, records from this study will be kept private unless law requires disclosure. No reports from this study will use your name or identify you personally.

Nonmilitary Subjects: All information that you provide as a part of this study will be confidential and will be protected to the fullest extent provided by law. Information that you provide and other records related to this study will be kept private, accessible only to those persons directly involved in conducting this study and to those individuals who provide oversight for human subjects protection. All questionnaires and test forms will be kept in a restricted access, locked cabinet while not in use. To enhance your privacy of the answers that you provide, data from questionnaires will be entered into a database in which individual responses are not identified. After verification of the database information, the hard copy of the questionnaires containing identifiers will be shredded.

Military subjects: All information that you provide as a part of this study will be confidential and will be protected to the fullest extent of the law. Information that you provide and other records related to this study will be kept private, accessible only to those individuals directly involved in conducting this study and members of the Uniformed Services University of the Health Sciences' Institutional Review Board and other Federal agencies who provide oversight for human use protection. All questionnaires and test forms will be kept in a restricted access, locked cabinet while not in use. However, please be advised that under Federal Law, a military member's confidentiality cannot be strictly guaranteed. To enhance your privacy of the answers that you provide, data from the test forms will be entered into a database in which individual responses are not identified. After verification of the database information, the hard copy of the questionnaires containing identifiers will be shredded.

****IF YOU HAVE ANY QUESTIONS PLEASE FEEL FREE TO ASK THEM****

I have read the explanation of this study on this form. The nature and purposes of the behavioral tasks have been reviewed and all my questions have been answered. I understand the nature of the study and I volunteer to participate in it. I attest that I meet the requirements for participation in this study. I understand that the study is designed for research purposes and not to be of direct benefit to me.

If you have any additional questions, you should contact Dr. Wendy A. Law of USUHS, Bethesda, Maryland 20814 at (301) 295-9678. She has agreed to discuss the study and any questions you may have regarding your participation in this research study. If you have questions about your rights as a research subject, you should call the Director of Research Programs in the Office of Research at USUHS (301-295-3303). This person is your representative and has no connection to the investigators conducting the studies.

The investigator will inform you of any significant new findings that develop during the course of the research that could in any way influence your willingness to continue your participation in the study. However, there is no risk to you for participating in this study and any findings are not expected to have any impact on the decision to participate.

By signing this informed consent, I am agreeing that the study has been explained to me and that I understand the study. I am signing that I agree to take part in this study but I may withdraw my consent to participate at any time without prejudice to future contacts with the USUHS. I will be provided a copy of this consent form.

I AGREE TO PARTICIPATE IN THE FOLLOWING PROCEDURES:

Brief Developmental and Educational History

Computer-Based Behavioral Tasks

Paper and Pencil Behavioral Tasks

NAME: _____

SIGNATURE: _____ **DATE:**_____

ADDRESS: _____

WITNESS NAME: _____

SIGNATURE: _____ **DATE:**_____

I certify that the research study has been explained to the above individual, by me or by my research staff, and that the individual understands the nature and purpose, the possible risks and benefits associated with taking part in this research study. Any questions that have been raised have been answered.

INVESTIGATOR: _____ **DATE:** _____

UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
4301 JONES BRIDGE ROAD
BETHESDA, MARYLAND 20814-4712
www.usuhs.mil

January 27, 2005

MEMORANDUM FOR LTJG JOHN R ASHBURN, , MEDICAL AND CLINICAL PSYCHOLOGY

SUBJECT: Uniformed Services University Institutional Review Board Continuation Approval (FWA # 00001628) of T072FZ for Human Subject Participation

Your Minimal Risk research protocol T072FZ, entitled ***"Confirmatory Analysis of Selected Computerized Measures: Divergent and Convergent Validity,"*** was reviewed and approved for continuation on January 21, 2005 by Edmund G. Howe, M.D., J.D., Chairperson, Institutional Review Board, under the provisions of 45 CFR 46.110(b)(1)Suppl. F(7). You are authorized to enroll up to 100 subjects in this study. **This approval expires on January 21, 2006.** This approval will be reported to the full Uniformed Services University IRB scheduled to meet on February 10, 2005.

The purpose of this study is to examine the relationships between selected traditional neuropsychological measures and computerized neuropsychological measures.

Data has been collected on 54 of the 80 subjects approved for accrual. Completion of data collection is anticipated by the end of March 2005. At present, no data have been analyzed. No adverse events were reported.

Authorization to conduct this protocol will automatically terminate on January 21, 2006. If you plan to continue data collection or analysis beyond this date IRB approval for continuation is required. Please submit a USU Form 3204A/B (application for continuing approval) to the Office of Research by **November** 22, **2005.** Though we will attempt to assist you by sending you a reminder, submission of an application for continuation is <u>your</u> responsibility. *Please note the termination date and the date for submission of your USU Form 3204 in your calendar!*

You are required to submit amendments to this protocol, changes to the informed consent document (if applicable), adverse event reports, and other information pertinent to human research for this project to this office for review. No changes to this protocol may be implemented prior to IRB approval. If you have questions regarding specific issues on your protocol, or questions of a more general nature concerning human participation in research, please contact me at 301-295-0819/9534 or mpickerel@usuhs.mil.

cc: Director,
Research
Administration
Chair, MPS
File

Margaret Pickerel
Institutional Review Board Coordinator

Appendix E

Measures, Scoring, and Brain Regions associated with Cognitive Domains

Table 1.1: Cognitive domains and associated brain regions

Cognitive Domain	**Brain Regions**
Attention	Reticular formation Parietal cortex Dorsolateral prefrontal cortex Cingulate (anterior)
Executive Functioning	Prefrontal/frontal lobes Cingulate (anterior)
Memory	Temporal lobes (bilateral) Prefrontal (bilateral)
Visuospatial Processing	Dorsal prefrontal area(s) Occipital lobes (bilateral)

(Cabeza & Nyberg, 2000; Andrewes, [2002], Chapter 4; Cabeza & Nyberg, 1997)

Table 1.2: Cognitive domains, WinSCAT tests, and scores

Cognitive Domain	**Test(s)**	**Scores**
Attention	Code Substitution	Response time Accuracy Throughput
Executive Functioning	Mathematical Processing Running Memory	Response time Accuracy Throughput
Memory	Delayed Code Substitution	Response time Accuracy Throughput
Visuospatial Processing	Match to Sample	Response time Accuracy Throughput

(Kabat et al., 2001; Bleiberg et al., 2000; Kane et al., 2005)

Table 1.3a: Study 1 - Cognitive domains, associated tests, and scores to be used for hypothesis 1

Cognitive Domain	**Tests**	**Score**
Attention	Digit Span Forward Symbol Search Stroop Color Task	Maximum number correct Total correct Time to completion
Executive Functioning	Digit Span Backward Letter Number Sequencing COWAT FAS COWAT Animals Stroop Color-Word Task	Maximum number correct Total correct Total errors Total errors Time to completion
Verbal Memory	CVLT short delay free recall CVLT long delay free recall WMS-III Logical Memory 1st WMS-III Logical Memory II WMS-III Logical Memory % retention	Total correct Total correct 1st trial total correct Raw score Raw score
Visuospatial Processing	Matrix Reasoning Rey-Osterrieth Complex Figure Test copy Picture Completion	Total correct Raw score Total correct
Verbal Learning	CVLT slope CVLT total WMS-III Logical Memory I	Raw score Raw score Raw score
Visual Memory	Rey-Osterrieth Complex Figure Delayed recall WMS-III FP I WMS-III FP II	Raw score Raw Score Raw Score
Language Expression	COWAT FAS COWAT Animals	Total correct Total correct
Problem Solving/Reasoning	WAIS-III Similarities Shipley Abstract Reasoning	Raw score Raw score

Table 1.3b: Study 1 - Cognitive domains, associated tests, and scores to be used for hypothesis 2

Cognitive Domain	**Tests**	**Score**
Attention	Digit Span Forward Symbol Search Stroop Color Task	Maximum number correct Total correct Time to completion
Executive Functioning	Digit Span Backward Letter Number Sequencing COWAT FAS COWATAnimals Stroop Color-Word Task	Maximum number correct Total correct Total errors Total errors Time to completion
Memory	CVLT short delay free recall CVLT long delay free recall WMS-III Logical Memory 1st WMS-III Logical Memory II WMS-III Logical Memory % retention CVLT slope CVLT total WMS-III Logical Memory I Rey-Osterrieth Complex Figure Delayed recall WMS-III FP I WMS-III FP II	Total correct Total correct 1st trial total correct Raw score Raw score Raw score Raw score Raw score Raw score Raw Score Raw Score
Visuospatial Processing	Matrix Reasoning Rey-Osterrieth Complex Figure Test copy Picture Completion	Total correct Raw score Total correct
Language Expression	COWAT FAS COWAT Animals	Total correct Total correct
Problem Solving/Reasoning	WAIS-III Similarities Shipley Abstract Reasoning	Raw score Raw score

Table 1.3c: Study 1 - Cognitive domains, associated tests, and scores to be used for hypothesis 3

Cognitive Domain	**Tests**	**Score**
Attention	Digit Span Forward	Maximum number correct
	Symbol Search	Total correct
	Stroop Color Task	Time to completion
Executive Functioning	Digit Span Backward	Maximum number correct
	Letter Number Sequencing	Total correct
	COWAT FAS + Animals	Total errors
	Stroop Color-Word Task	Time to completion
Memory	CVLT short delay free recall	Total correct
	CVLT long delay free recall	Total correct
	WMS-III Logical Memory 1st	1st trial total correct
	WMS-III Logical Memory II	Raw score
	WMS-III Logical Memory % retention	Raw score
	CVLT slope	Raw score
	CVLT total	Raw score
	WMS-III Logical Memory I	Raw score
	Rey-Osterrieth Complex Figure Delayed recall	Raw score
	WMS-III FP I	Raw Score
	WMS-III FP II	Raw Score
Visuospatial Processing	Matrix Reasoning	Total correct
	Rey-Osterrieth Complex Figure Test copy	Raw score
	Picture Completion	Total correct

Table 1.4: Study 2 - Cognitive domains, associated tests, and score to be used in all three hypotheses

Cognitive Domain	**Tests**	**Score**
Attention	Digit Span Forward Digit Symbol TMT Part A	Total correct Total correct Time to completion
Executive Functioning	Digit Span Backward Stroop Color-Word Task PASAT Trials 1 and 2	Total correct Time to completion Total correct
Memory	RAVLT I and II Verbal Paired Associates I & II Digit Symbol Incidental Recall	Total correct Total correct Total correct
Visuospatial Processing	Matrix Reasoning Block Design Figural Memory	Total correct Total correct Total correct

Table 1.5: Study 2 additional tests administered

Cognitive Domain	**Tests**	**Score**
General Intellectual Functioning (covariate)	Shipley	t-score
Simple Motor Skills (covariate)	Grooved Pegboard	Dominant hand t-score
(Attention, Executive Functioning, and motor processing)	Stroop Color Symbol Search Letter-Number Sequencing TMT B	n/a (results not being analyzed)

(Lezak, 1995; pages 121-126; Chapters 9-16)

Appendix F

TELEPHONE SCRIPT FOR THE WINSCAT STUDY

"Hello, this is _____ calling from the Uniformed Services University. I am calling regarding your interest in a research study concerning the relationship between paper-and-pencil and computer-based measures. Do you have about 10 minutes for me to tell you about the study?"

Yes - continue
No - "OK. Is there a better time that I may call you to tell you more about the study?"

Yes - Write down time and date _____
No - "Thank you for your time"

"The purpose of this study is to investigate the similarities and differences of different types of thinking measures, and the impact of using different means of administering these measures. We are interested in this topic to better understand the relationship between various ways of evaluating thinking skills. The study involves one session that will take about 2 hours."

"If you agree to participate, you will be asked to come to the Neurocognitive Laboratory at the USUHS/Navy Medical complex campus or LT Ashburn's office in the Behavioral Health Department at the National Naval Medical Center. If you cannot come to either of these locations, a location that is more convenient for you will try to be located. The study consists of a question-and-answer session that the examiner will use to fill out a questionnaire, and completing some paper-and-pencil and computer-based measures."

"Do you have any questions?"

"You will receive $30 for your time in this research unless you are an active-duty service member, in which case we cannot pay you for this study."

"Do you think that you would like to participate in this study?"

No - "OK. Thank you for your time"
Yes - "OK, I have some questions I need to ask you to determine your eligibility to participate in this study."

1. What is your birth date?. _____(18 = Must be before date 1985; check month/day with current month/day for an exact determination)

   If birthday is AFTER Date 1985 "You must be at least 18 years of age to participate in this study. Thank you for your time."

   If birthday BEFORE Date 1983 - continue

2. "Do you have any difficulties or disabilities that interfere with reading in English, speaking in English, or hearing?"

   No - continue
   Yes - "What are those difficulties?"_____

   If not easily resolved "This study is would not be appropriate for you. Thank you for your interest and time."

   If easily resolved (e.g., use of a hearing aid) – continue

3. "Are you active duty military?"

   No - continue
   Yes – "No payment is possible for military personnel, and you must use TDY or liberty time to participate (unless you can make arrangements with your supervisor to participate during normal working hours). Are you still interested in the study?"

   No – "Thank you for your time."
   Yes – continue

4. "Are you currently taking any medications on a regular basis?"

   No - continue
   Yes – "what medication do you take?"_____

   If medication is a psychotropic drug or opiate (anxiolytic, antidepressant, mood stabilizer, antipsychotic, methodone, opiate pain killers) "You do not meet the requirements for participation in this study, but thank you for your time and interest."

5. "Have you ever been diagnosed with any of the following health conditions?"

   __Flashbacks/PTSD
   __Panic Attacks/Disorder
   __Schizophrenia
   __Anxiety/Depression
   __Substance Abuse
   ___Bipolar Disorder/Manic Depression
   __Any neurological disorder

   __Any other health problems?

   _____

No - continue
Yes (to any) – "Are you currently receiving treatment for this diagnosis or health problem?"

Yes – "You do not meet the requirements for participation in this study, but thank you for your time and interest."
No - continue

6. "Have you ever had a head injury that resulted in a loss of consciousness?"

No - continue
Yes – "You do not meet the requirements for participation in this study, but thank you for your time and interest."

7. "This study requires the use of a computer mouse. Do you have any condition that prevents you from using a computer mouse without difficulty?"

No - continue
Yes – "You do not meet the requirements for participation in this study, but thank you for your time and interest."

"OK, it looks like you are eligible for this study. Now I need to schedule a two-hour block of time to meet with you to do the protocol. Is there a particular day and time that works well for you? <Make note in log> Is it more convenient for you to come to USUHS, the National Naval Medical Center, or would you like to do the protocol at another location?" <Make note in log> <Give or get directions, as indicated>

"I want to make sure I have information to be able to contact you." and provide a reminder for your appointment."
Name:_____
Mailing
Address:_____
_____
Phone numbers: Home_____ Work_____
Cell/Pager_____
Email:_____
Best way to reach_____ best time of day to call_____

<If testing is to be completed on base AND subject is not a military member or dependant>

"Because of increased security on the base, I need to have your social security number and drivers license number so the guard at the gate will let you in."
SSN_____ DLN_____

"Would you like a reminder for this appointment? What is the best way to get this to you?"

Circle: Y N _____

"Because of our research schedule, it is important that you arrive at the lab on time. Please call us at _____ if you anticipate any problems with keeping your appointment. Thank you and we look forward to seeing you on _____ (date) at _____ (time)."

Other notes:

(Note: Screen adapted from Chavez, 2001)

Appendix G

Developmental and Educational History Questionnaire

Brief Developmental and Educational History (please check only one answer per question):

Which hand do you write with *most often*?

___ Right hand
___ Left hand
___ Either (no preference)

Were you ever forced to switch from using your left hand to using your right hand for any activities?

___ Yes
___ No

Do any of your immediate biological family members (parents, siblings, children) write most often with the left-hand?

___ Yes
___ No

Please indicate your relative rate in achieving developmental milestones during childhood, using the following scale:

1 somewhat later than others **2** average **3** earlier than others **4** unknown

___ Walking
___ Talking
___ Socializing
___ Toileting

Have you ever been evaluated, treated, or diagnosed with a learning disability?

___ Yes
___ No

Have you ever been evaluated, treated, or diagnosed with an attention deficit hyperactivity disorder?

___ Yes
___ No

Have any members of your immediate biological family (parents, siblings, children) ever been diagnosed with a learning disability or with attention deficit/hyperactivity disorder?

___ Yes

___ No

Did you repeat any grades in elementary school?
___ Yes (if yes, which grade(s))?
___ No

What were your average grades in high school?
___ As and Bs
___ Bs and Cs
___ Cs and Ds
___ Ds and Fs
___ Other (describe:_____)

Please indicate how easy or hard it was for you to learn the basic high school subject areas, using the following scale:

1 (hard) **2** (average) **3** (easy) **4** (not taken)

___ English
___ History/Social Studies
___ Geography
___ Mathematics
___ Algebra
___ Geometry
___ Science
___ Biology
___ Chemistry
___ Physics
___ Art
___ Music

What is the highest level of education you have completed?

___ High School Diploma/GED
___ Some college
___ College Associates (2-year) degree
___ Technical/Vocational certification
___ College/University (4-year) degree
___ Master's degree
___ Law, MD, PhD degree

Additional information:

How many times have you been hospitalized?

___ 0 (never)
___ 1

___ 2
___ 3 or more

(If more than 0, please provide year(s) of hospitalization and primary reason):

(If above > 1) How many times have you been hospitalized because of an injury to your head?

___ 0 (never)
___ 1
___ 2
___ 3 or more

How many times have you had a head injury with which you became dizzy, developed a headache, or were knocked unconscious? (e.g., sports activity, motor vehicle accident, slip and fall, assault)

___ 0 (never)
___ 1
___ 2
___ 3 or more

How many times have you had a seizure or convulsion? (including high fevers in childhood, head injuries, etc.)?

___ 0 (never)
___ 1
___ 2
___ 3 or more

Appendix H

USUHS Employee Volunteer Form

Employees as Research Volunteers

The following information is being provided to you because you are a civilian employee of the DoD and you have expressed an interest in volunteering to participate in a research protocol conducted at USUHS.

According to ***USUHS Instruction 3201***, the following guidelines apply to employees who wish to participate as volunteers in research protocols conducted at USUHS:

a. Employees

(1) When civilian employees of the DoD volunteer to participate in a research protocol, the following provisions will apply:

(a) Any duty as a volunteer performed during the employee's regularly scheduled duty will be considered constructive duty for which straight time rates apply. ***Employees must have the approval of their immediate supervisor to participate during any time***;

(b) Participation outside an employee's regularly scheduled duty or during leave is not considered duty time. If compensated, the employee must take leave or participate in the study at a normally scheduled break. Off duty employment qualifications must be followed.

(c) The employee will be informed of the above.

(2) Solicitation and selection of employees will not suggest coercion or preferential treatment.

(3) Generally, investigators will not use employees under their supervision as research subjects. ***However, if an employee wishes to participate in his or her supervisor's study, the employee may seek the approval of the IRB Chair or IRB Executive Secretary.***

By signing this form below, you are confirming the following:

- You are a civilian employee of DoD who is interested in volunteering to participate in a research protocol conducted at USUHS.
- The research protocol for which are interested in participating, has been thoroughly and explicitly explained to you, including the informed consent process and the risks/benefits associated with the study.
- You have not been coerced or promised preferential treatment in any way for your participation as a volunteer in a research protocol.
- You have obtained the permission of your immediate supervisor to participate as a volunteer in a research protocol during your normal duty time ***(If you are participating in your immediate supervisor's study this form must also be signed by the IRB Chair or the IRB Executive Secretary in room A-1032).***

Protocol Title	Name of Principal Investigator
Signature of Participant	Date
Signature of IRB Chair or IRB Exec. Secretary ***(if required)***	Date

Appendix I

WinSCAT Review and Instructions
Review of WinSCAT Tests

Test 1. CODE SUBSTITUTION:

Description: This test measures visual focused attention and scanning. The participant is required to examine a target symbol-digit pair that is presented visually on the computer screen and to compare the target pair with a test symbol-digit pair that is provided in a simultaneous visual array of nine symbol-digit pairs in numeric order (1 to 9). On each trial, all nine of the test symbol-digit pairs are presented in an array on the top portion of the screen, and a new target symbol-digit pair is presented centrally in the bottom portion of the screen. The instructions direct the participant to press the index-finger mouse key if the target symbol-digit pair matches the test symbol-digit pair in the visual array, and to press the second- finger mouse key if the target pair differs from the test pair in the array. The instructions emphasize the importance of both speed and accuracy and also inform the participant that a memory test of the array test symbol-digit pairs will be presented later in the session (i.e., Test 5). Within each session, the test symbol-digit pairs in the array remain the same across each trial. However, the nine symbols and numbers will be paired differently for each subsequent test session, thereby eliminating any performance improvement effects from learning the specific symbol-digit testing pairs over repeated sessions.

Test 2. RUNNING MEMORY:

Description: This test measures visual sustained attention and working memory. For several minutes continuously, individual numbers are successively displayed on the screen at a central visual focal point. The participant is instructed to press the index-finger mouse key if the presented number matches the immediately previous letter, and to press the second finger mouse key if the presented number differs from the immediately previous letter. Several different sequence series rotate through the program, with a new sequence triggered by the participant's unique identification number. This procedure is designed to eliminate performance improvement effects over repeated sessions that could have been due to learning a specific sequencing of the numbers.

Test 3. MATHEMATICAL PROCESSING:

Description: This test measures speeded arithmetic calculation ability (single digit addition and subtraction). Simple two-step linear arithmetic problems are presented one at a time on the screen (e.g., 5 + 6 - 3 = ?). The participant is instructed to press the index finger mouse key if the solution to the visually-presented arithmetic problem is less than "5", and to press the second finger mouse key if the solution to the visually-presented arithmetic problem is more than "5". As with the previous tests, the problems change from session to session, eliminating any implicit memory for the correct sequencing of "less than 5/more than 5" responses on subsequent sessions.

Test 4. MATCHING TO SAMPLE:

Description: This test measures spatial perception and immediate visual memory recognition for designs presented in an organized 4 by 4 box frame. For each trial, the

participant is briefly shown a single 4 by 4 target design presented in the center of the monitor. The single design disappears and, after a brief delay, is replaced by two designs presented simultaneously in a side-by-side orientation on the screen. The participant is instructed to press the index finger mouse key if the left-most design from the pair is identical with the previous single target design, and to press the second finger mouse key if the design on the right is identical with the previous target design. Once again, there are several versions available that alternate according to the participant's unique identification number so that no two consecutive sessions present the exact same designs and choices to a given participant.

Test 5. DELAYED CODE SUBSTITUTION (MEMORY):

Description: This test presents a series of single symbol-digit pairs, as in Test 1, but without presenting the nine test pairs from the visual array. The participant is instructed to press the index finger mouse key if the target symbol-digit pair is the same as the test pair for that digit that had been presented in the visual array during Test 1, and to press the second finger mouse key if the target pair differs from the test pair that was presented previously in the array. Because this is a learning/memory test, there is no practice trial.

WinSCAT Test Instructions:

Test 1: Code Substitution

IN THIS TEST YOU WILL SEE A ROW OF SYMBOLS AND ROW OF NUMBERS. EACH NUMBER HAS ITS OWN SYMBOL THAT APPEARS IN THE BOX ABOVE IT. *(Point to screen in expected location of the model)*

BELOW THE ROW OF SYMBOL AND NUMBER PAIRS WILL BE A SAMPLE BOX WITH ONE SYMBOL AND ONE NUMBER PAIR.

PRESS THE "1" BUTTON IF THE SYMBOL/NUMBER PAIR IN THE SAMPLE BOX IS THE SAME AS THE CORRESPONDING SYMBOL/NUMBER PAIR IN THE ROWS ABOVE IT.

PRESS THE "2" BUTTON IF THE SYMBOL/NUMBER PAIR IN THE SAMPLE BOX IS NOT THE SAME AS THE CORRESPONDING SYMBOL/NUMBER PAIR IN THE ROWS ABOVE IT.

REMEMBER THAT YOU WILL BE ASKED TO RECALL THE SYMBOL/NUMBER PAIRS FROM THE ROWS, SO TRY TO LEARN THEM DURING THESE TESTS.

BE AS QUICK AS YOU WITHOUT MAKING MISTAKES.

Test 2: Running Memory

IN THIS TASK, NUMBERS WILL BE DISPLAYED ONE AT A TIME ON THIS SCREEN *(Point to middle of screen).*

IMMEDIATELY AFTER THE FIRST NUMBER, PRESS THE "1" BUTTON IF THE NEXT NUMBER IS THE SAME AS THE NUMBER THAT CAME RIGHT BEFORE IT.

PRESS THE "2" BUTTON IF THE NUMBER IS DIFFERENT THAN THE ONE THAT CAME BEFORE IT. DO NOT PRESS A BUTTON WHEN THE VERY FIRST NUMBER APPEARS.

REMEMBER TO PRESS A BUTTON FOR EACH NUMBER THAT OCCURS AFTER THE VERY FIRST NUMBER. *(make certain that the participant remembers what the task requires, with a response for every single number after the very first one)*

REMEMBER TO RESPOND AS FAST AS YOU CAN WITHOUT MAKING MISTAKES.

Test 3: Mathematical Processing

THIS TASK ASKS YOU TO SOLVE SIMPLE ARITHMETIC PROBLEMS THAT WILL BE PRESENTED ON THIS SCREEN *(point)* **ONE AT A TIME.**

LOOKING AT EACH PROBLEM, AND DECIDE IF THE ANSWER IS LESS THAN "5" OR MORE THAN "5". PRESS THE "1" BUTTON IF THE ANSWER TO THE PROBLEM IS LESS THAN 5, AND PRESS THE "2" BUTTON IF THE ANSWER IS MORE THAN 5.

SOLVE THE PROBLEMS AS FAST AS YOU CAN WITHOUT MAKING MISTAKES.

Test 4: Matching to Sample

FOR THIS TASK, A LARGE BOX WITH RED AND WHITE COLORED SQUARES WILL BE DISPLAYED HERE ON THE SCREEN *(point)* **FOR A BRIEF PERIOD AND THEN IT WILL DISAPPEAR.**

AFTER A FEW SECONDS, A PAIR OF BOXES WILL APPEAR SIDE BY SIDE ON THE SCREEN *(point to the left and right locations where the boxes will be displayed).*

PRESS THE "1" BUTTON IF THE BOX ON THE LEFT SIDE *(point)* **MATCHES THE FIRST BOX THAT YOU SAW, OR PRESS THE "2" BUTTON IF THE RIGHT BOX** *(point)* **MATCHES THE FIRST BOX.**

REMEMBER TO ANSWER AS FAST AS POSSIBLE WITHOUT MAKING MISTAKES.

Test 5: Delayed Code Substitution

IN THIS TASK, YOU WILL SEE SIMPLE PAIRS OF SYMBOLS AND NUMBERS.

PRESS THE "1" BUTTON IF THE PAIR CORRECTLY MATCHES THE PAIR IN THE ROWS FROM THE FIRST SYMBOL/NUMBER TEST.

PRESS THE "2" BUTTON IF THE PAIR DOES NOT MATCH THE PAIR IN THE ROWS FROM THE FIRST TEST.

ANSWER AS FAST AS POSSIBLE WITHOUT MAKING MISTAKES.

Appendix J

Rapport Scale

On a scale of 1 to 10 how you would best describe the tester:

Aloof ---------- Friendly

Anxious ---------- Calm

Bored ---------- Attentive

Annoying ---------- Enjoyable

Critical ---------- Encouraging

Mean score:

Table 1

Subject Demographics

Variable	yrs/%	Total (N = 99)
Age (yrs)		
Mean	28.66	
SD	5.72	
Gender (%)		
Male	70.30	70
Female	29.70	29
Ethnicity (%)		
Caucasian	71.70	71
African American	11.10	11
Hispanic	7.10	7
Asian American	4.00	4
Native American	0.00	0
Pacific Islander	3.00	3
Other	3.00	3
Education (%)		
High School (=<12)	14.10	14
Part college (>12, <16)	25.30	25
College grad (=16)	16.20	16
Post-grad (>16)	44.40	44

Table 2

Correlations among traditional neuropsychological attention measures (N=99; Digit Span, maximum forward span, Symbol Search, raw score, and Stroop Neuropsychological Screening Test, color times)

Attention Measures	DSF	SSRS
DSF	-	
SSRS	.32*	-
STRPC	-.38*	-.51*

Note. DSF = Digit Span maximum forward span, SSRS = Symbol Search raw score, STRPC = Stroop Neuropsychological Screening Test Color trial time to completion.

*p < .05

Table 3

Correlations among traditional neuropsychological executive functioning measures (N=99, Digit Span, maximum backward span, Letter Number raw score, COWAT total errors, TMT part B, CVLT preservation raw score, WCST failure to maintain set, Stroop Neuropsychological Screening Test, Color Word, time to completion)

Executive Functioning Measures	DSB	LNRS	CWTTE	TMTB	CVLTPR	WCSTFS
DSB	-					
LNRS	.57*	-				
CWTTE	-.12	-.04	-			
TMTB	-.34*	-.39*	-.07	-		
CVLTPR	-.29*	-.26*	.24*	.12	-	
WCSTFS	.01	-.03	-.06	-.01	-.02	-
STRPCW	-.19*	-.27*	-.08	.46*	.26*	.04

Note. DSB = Digit Span backward, LNRS = Letter Number raw score, CWTTE = Controlled Oral Word Association Test total errors, TMTB = Trail Making Test part B, CVLTPR = California Verbal Learning Test preservation raw score, WCSTFS = Wisconsin Card Sort Test failure to maintain set, STRPCW = Stroop Neuropsychological Screening Test, color word.

*p < .05

Table 4

Correlations among traditional neuropsychological verbal memory measures (N=99, California Verbal Learning Test Short Delay Free Recall and Long Delay Free Recall raw scores, WMS-III Logical Memory (LM) 1st trial raw score, LMII raw score and LM percent retention raw score)

Verbal Memory Measures	CVLTSD	CVLTLD	LM1ST	LMII
CVLTSD	-			
CVLTLD	.89*	-		
LM1ST	.43*	.38*	-	
LMII	.46*	.44*	.82*	-
LMPR	.18*	.18*	.26*	.49*

Note. CVLTSD = California Verbal Learning Test Short Delay Free Recall, CVLTLD = California Verbal Learning Test Long Delay Free Recall, LM1ST = Logical Memory 1st trail raw score, LMII = Logical Memory II raw score, LMPR = Logical Memory percent retention raw score.

*$p < .05$

Table 5

Correlations among traditional neuropsychological visuospatial processing measures (N=99, WAIS-III Matrix Reasoning raw score, Rey-Osterrieth Complex Figure Test copy raw, WAIS-III Picture Completion raw score)

Visuospatial Processing Measures	MXRS	ROCFTR
MXRS	-	
ROCFTR	.27*	-
PCRS	.39*	.31*

Note. MXRS = Matrix Reasoning raw score, ROCFTR = Rey-Osterrieth Complex Figure Test copy raw, PCRS = Picture Completion raw score.

*$p < .05$

Table 6

Correlations among traditional neuropsychological verbal learning measures (N=99, CVLT-II slope raw score, CVLT-II total correct raw score, WMS-III LMI raw score)

Verbal Learning Measures	CVLTSL	CVLTIIR
CVLTSL	-	
CVLTIIR	.20*	-
LMIR	.03	.49*

Note. CVLTSL = California Verbal Learning Test slope raw score, CVLTIIR = California Verbal Learning Test II raw score, LMIR = Logical Memory I raw score.

*p < .05

Table 7

Correlations among traditional neuropsychological visual memory measures (N=99, ROCF delayed recall raw score, WMS-III Family Pictures I and II raw scores)

Visual Memory Measures	ROCFDR	FPI
ROCFDR	-	
FPI	.46*	-
FPII	.45*	.98*

Note. ROCFDR = Rey-Osterrieth Complex Figure Test delayed recall raw score, FPI = Family Pictures I raw score, FPII = Family Pictures II raw score.

*p < .05

Table 8

Correlations among traditional neuropsychological language expression measures (N=99, Controlled Oral Word Association Test Letters (FAS) total correct and Categories (Animals) total correct)

Language Expression Measures	FAS
FAS	-
ANIM	.47*

Note. FAS = Controlled Oral Word Association Test Letters total correct, ANIM = Controlled Oral Word Association Test Letters Categories total correct.

*p < .05

Table 9

Correlations among traditional neuropsychological problem-solving measures (N=99, WAIS-III Similarities raw score, Shipley Abstract Reasoning raw score)

Problem Solving Measures	SIM
SIM	-
SHIPAR	.37*

Note. SIM = Similarities raw score, SHIPAR = Shipley Abstract Reasoning raw score.

*p < .05

Table 10

Correlations of traditional neuropsychological measures across six domains (1 – 6) with computerized measures (CDLTP, RMTP, M2STP, MTHTP, CDDTP)

	CDLTP	RMTP	M2STP	MTHTP	CDDTP
1. DSF	***.40****	.38*	.28*	.20	.06
SSRS	***.41****	.41*	.39*	.35*	.04
STRPC	***-.26****	-.40*	.04	-.34*	.01
2. DSB	.32*	***.33****	.12	***.27****	.27*
LNRS	.39*	***.34****	.27*	***.37****	.18
CWTTE	-.13	***.01***	-.06	***.10***	-.24*
TMTB	-.52*	***-.41****	-.28*	***-.56****	-.27*
CVLTRS	-.11	***-.11***	-.10	***-.21****	-.14
WCSTFS	-.01	***.06***	-.09	***-.10***	.26*
STRPCW	-.41*	***-.38****	-.07	***-.48****	-.14
3. CVLTSD	.21*	.15	.03	.32**	***.33****
CVLTLD	.09	.08	.04	.23*	***.30****
LM1ST	.38*	.09	-.03	.37*	***.38****
LMII	.44*	.15	.23*	.36*	***.40****
LMPR	.16	-.06	.05	.05	***.23****
CVLTSL	-.02	.11	-.02	.02	***-.05***
CVLTIIR	.14	.12	.05	.20	***.32****
LMIR	.45*	.13	.12	.38*	***.43****
ROCFDR	.40*	.21*	.41*	.15	***.52****
FPI	-.02	.02	.18	.04	***.19***
FPII	-.05	.02	.16	.06	***.19***
4. MXRS	.31*	.23*	***.12***	.30*	.19
ROCFTR	.08	-.01	***.19***	.00	.28*
PCRS	.17	.04	***.06***	.27*	.17
5. FAS	.01	.03	-.07	.25*	.16
ANIM	-.10	.03	-.07	.05	.13
6. SIM	.22*	.07	-.03	.30*	.11
SHIPAR	.42*	.06	-.01	.38*	.31*

Note. Expected relations between traditional and computerized measures are in shaded italicized bold font; CDLTP=Computerized code substitution learning throughput (TP) score, RMTP=Computerized running memory TP score, M2STP=Computerized match-to-sample TP score, MTHTP=Computerized math TP score, CDDTP=Computerized code substitution delayed memory TP score, 1=traditional neuropsychological attention domain measures, 2=traditional neuropsychological executive functioning domain measures, 3=traditional neuropsychological memory domain measures, 4=traditional neuropsychological visuospatial domain measures, 5=traditional neuropsychological language expression domain measures, 6=traditional neuropsychological problem-solving domain measures. The names of the specific traditional neuropsychological measures represented in this table have been explained in Tables 2 – 9.

*$p < .05$

Table 11a

Relationships of demographic variables, intellectual functioning measure (Shipley t-score), and motor performance task, dominant hand (Grooved Pegboard t-score) with WinSCAT computerized measure Code Substitution Learning throughput score (CDLTP)

	t-test		ANOVA		Pearson Correlation	
	t	P	F	P	r	P
1. Age	-	-	-	-	-.35	.05
Gender	-1.56	ns	-	-	-	-
Ethnicity	-	-	.30	ns	-	-
Education	-	-	-	-	.48	.05
2. Shipley	-	-	-	-	.43	.05
3. Grooved Pegboard	-	-	-	-	.26	.05

Note. Age, education, Shipley, and Grooved Pegboard were all analyzed using bivariate correlations. Gender was analyzed using an independent samples t-test. Ethnicity was analyzed using analysis of variance (ANOVA) using three groups (Caucasian, African-American, and all others combined).

Table 11b

Relationships of demographic variables, intellectual functioning measure (Shipley t-score), and motor performance task, dominant hand (Grooved Pegboard t-score) with WinSCAT computerized measure Running Memory throughput score (RMTP)

	t-test		ANOVA		Pearson Correlation	
	t	P	F	P	r	P
1. Age	-	-	-	-	-.29	.05
Gender	-.56	ns	-	-	-	-
Ethnicity	-	-	.07	ns	-	-
Education	-	-	-	-	.47	.05
2. Shipley	-	-	-	-	.07	ns
3. Grooved Pegboard	-	-	-	-	.16	ns

Note. Age, education, Shipley, and Grooved Pegboard were all analyzed using bivariate correlations. Gender was analyzed using an independent samples t-test. Ethnicity was analyzed using analysis of variance (ANOVA) using three groups (Caucasian, African-American, and all others combined).

Table 11c

Relationships of demographic variables, intellectual functioning measure (Shipley t-score), and motor performance task, dominant hand (Grooved Pegboard t-score) with WinSCAT computerized measure Mathematical processing throughput (MTHTP)

	t-test		ANOVA		Pearson Correlation	
	t	P	F	P	r	P
1. Age	-	-	-	-	.11	ns
Gender	-2.01	.05	-	-	-	-
Ethnicity	-	-	.47	ns	-	-
Education	-	-	-	-	.56	.05
2. Shipley	-	-	-	-	.42	.05
3. Grooved Pegboard	-	-	-	-	.16	ns

Note. Age, education, Shipley, and Grooved Pegboard were all analyzed using bivariate correlations. Gender was analyzed using an independent samples t-test. Ethnicity was analyzed using analysis of variance (ANOVA) using three groups (Caucasian, African-American, and all others combined).

Table 11d

Relationships of demographic variables, intellectual functioning measure (Shipley t-score), and motor performance task, dominant hand (Grooved Pegboard t-score) with WinSCAT computerized measure Match-to-Sample throughput score (M2STP)

	t-test		ANOVA		Pearson Correlation	
	t	P	F	P	r	P
1. Age	-	-	-	-	-.18	ns
Gender	.01	ns	-	-	-	-
Ethnicity	-	-	2.14	ns	-	-
Education	-	-	-	-	.19	ns
2. Shipley	-	-	-	-	.12	ns
3. Grooved Pegboard	-	-	-	-	.02	ns

Note. Age, education, Shipley, and Grooved Pegboard were all analyzed using bivariate correlations. Gender was analyzed using an independent samples t-test. Ethnicity was analyzed using analysis of variance (ANOVA) using three groups (Caucasian, African-American, and all others combined).

Table 11e

Relationships of demographic variables, intellectual functioning measure (Shipley t-score), and motor performance task, dominant hand (Grooved Pegboard t-score) with WinSCAT computerized measure Code Substitution Delayed Memory throughput score (CDDTP)

	t-test		ANOVA		Pearson Correlation	
	t	P	F	P	r	P
1. Age	-	-	-	-	-.24	ns
Gender	-1.21	ns	-	-	-	-
Ethnicity	-	-	.03	ns	-	-
Education	-	-	-	-	.19	ns
2. Shipley	-	-	-	-	.35	.05
3. Grooved Pegboard	-	-	-	-	.19	ns

Note. Age, education, Shipley, and Grooved Pegboard were all analyzed using bivariate correlations. Gender was analyzed using an independent samples t-test. Ethnicity was analyzed using analysis of variance (ANOVA) using three groups (Caucasian, African-American, and all others combined).

Table 12

Four Block Hierarchical Linear Regression Model with Code Substitution Learning predicting an index score of Attention

Model and Variables	Unadjusted R^2	Adjusted R^2	R^2 Change	sr	**B**	***SE B***	β
(Block 1 – Demographic Variables)	.26*	.24*	.26*				
Age				-.25	-.04	.02	-.25*
Gender				.16	.29	.17	.16
Education				.46	.15	.03	.47*
(Block 2 – Intellectual Functioning)	.29*	.26*	.03				
Shipley Score				.16	.02	.01	.18
(Block 3 – Motor Performance)	.30*	.26*	.00				
Grooved Pegboard dominant hand				.10	.01	.01	.11
(Block 4 – Computerized Measure)	.39*	.34*	.09*				
Code Substitution Learning				.30	.03	.01	.41*

Notes. Final N = 84. sr = semi-partial correlation, the square of which describes the percent variance accounted for by each predictor after accounting for previously-entered control variables. **B** = beta coefficient, which indicates the standardized strength of the relationship between the predictor variable and outcome variable. ***SE B*** = standardized error of the beta value, which equals the error term for the beta. β = partial correlation, which describes the percent account for by each predictor without accounting for the inclusion of previous predictor variables.

*$p < .05$

Table 13

Four Block Hierarchical Linear Regression Model with Math Processing predicting an index score of Executive Functioning

Model and Variables	Unadjusted R^2	Adjusted R^2	R^2 Change	sr	**B**	***SE B***	β
(Block 1 – Demographic Variables)	.22*	.18*	.22*				
Age				-.12	-.01	.01	-.12
Gender				.02	.02	.12	.02
Education				.46	.09	.02	.46*
(Block 2 – Intellectual Functioning)	.24*	.18*	.02				
Shipley Score				.13	.02	.02	.15
(Block 3 – Motor Performance)	.25*	.18*	.01				
Grooved Pegboard dominant hand				-.11	-.01	.01	-.12
(Block 4 – Computerized Measure)	.29*	.21*	.05				
Math Processing				.21	.02	.01	.29

Notes. Final N = 57. sr = semi-partial correlation, the square of which describes the percent variance accounted for by each predictor after accounting for previously-entered control variables. **B** = beta coefficient, which indicates the standardized strength of the relationship between the predictor variable and outcome variable. ***SE B*** = standardized error of the beta value, which equals the error term for the beta. β = partial correlation, which describes the percent account for by each predictor without accounting for the inclusion of previous predictor variables.

*$p < .05$

Table 14

Four Block Hierarchical Linear Regression Model with Running Memory predicting an index score of Executive Functioning

Model and Variables	Unadjusted R^2	Adjusted R^2	R^2 Change	sr	**B**	***SE B***	β
(Block 1 – Demographic Variables)	.22*	.18*	.22*				
Age				-.12	-.01	.01	-.12
Gender				.02	.02	.12	.02
Education				.46	.09	.02	.46*
(Block 2 – Intellectual Functioning)	.24*	.18*	.02				
Shipley Score				.13	.02	.02	.15
(Block 3 – Motor Performance)	.25*	.18*	.01				
Grooved Pegboard dominant hand				-.11	-.01	.01	-.12
(Block 4 – Computerized Measure)	.33*	.26*	.09*				
Running Memory				.29	.01	.00	.36*

Notes. Final N = 57. sr = semi-partial correlation, the square of which describes the percent variance accounted for by each predictor after accounting for previously-entered control variables. **B** = beta coefficient, which indicates the standardized strength of the relationship between the predictor variable and outcome variable. ***SE B*** = standardized error of the beta value, which equals the error term for the beta. β = partial correlation, which describes the percent account for by each predictor without accounting for the inclusion of previous predictor variables.

*$p < .05$

Table 15

Four Block Hierarchical Linear Regression Model with Code Substitution Delayed Memory predicting an index score of Memory

Model and Variables	Unadjusted R^2	Adjusted R^2	R^2 Change	sr	**B**	***SE B***	β
(Block 1 – Demographic Variables)	.17*	.14*	.17*				
Age				-.20	.15	.12	-.20*
Gender				.30	.43	.15	.30*
Education				.23	.06	.03	.23*
(Block 2 – Intellectual Functioning)	.37*	.34*	.20*				
Shipley Score				.45	.06	.01	.50*
(Block 3 – Motor Performance)	.37*	.33*	.00				
Grooved Pegboard dominant hand				.04	.00	.01	.05
(Block 4 – Computerized Measure)	.44*	.40*	.07*				
Code Substitution Delayed Memory				.27	.01	.00	.30*

Notes. Final N = 86. sr = semi-partial correlation, the square of which describes the percent variance accounted for by each predictor after accounting for previously-entered control variables. **B** = beta coefficient, which indicates the standardized strength of the relationship between the predictor variable and outcome variable. ***SE B*** = standardized error of the beta value, which equals the error term for the beta. β = partial correlation, which describes the percent account for by each predictor without accounting for the inclusion of previous predictor variables.

*$p < .05$

Table 16

Four Block Hierarchical Linear Regression Model with Match-to-Sample predicting an index score of Visuospatial Processing

Model and Variables	Unadjusted R^2	Adjusted R^2	R^2 Change	sr	**B**	***SE B***	β
(Block 1 – Demographic Variables)	.03	.00	.03				
Age				-.08	-.01	.01	-.08
Gender				.08	.14	.17	.08
Education				.16	.05	.03	.16
(Block 2 – Intellectual Functioning)	.40*	.37*	.36*				
Shipley Score				.60	.09	.01	.68*
(Block 3 – Motor Performance)	.42*	.38*	.02				
Grooved Pegboard dominant hand				.14	.01	.01	.15
(Block 4 – Computerized Measure)	.43*	.39*	.01				
Match-to-Sample				.10	.01	.01	.11

Notes. Final N = 89. sr = semi-partial correlation, the square of which describes the percent variance accounted for by each predictor after accounting for previously-entered control variables. **B** = beta coefficient, which indicates the standardized strength of the relationship between the predictor variable and outcome variable. ***SE B*** = standardized error of the beta value, which equals the error term for the beta. β = partial correlation, which describes the percent account for by each predictor without accounting for the inclusion of previous predictor variables.

*$p < .05$

Table 17

Subject Demographics

Variable	yrs/%	Total (N = 72)
Age (yrs)		
Mean	36.10	
SD	15.09	
Gender (%)		
Male	37.50	27
Female	62.50	45
Ethnicity (%)		
Caucasian	79.17	57
African American	13.89	10
Asian American	4.17	3
Native American	1.39	1
Other	1.39	1
Education (%)		
High School (=<12)	4.17	3
Part college (>12, <16)	20.84	15
College grad (=16)	40.28	29
Post-grad (>16)	34.72	25

Table 18

Correlations among traditional neuropsychological attention measures (N=72; WAIS-III Digit Span, forward, total correct, WAIS-III Digit Symbol Coding, total correct, and Trail Making Test, Part A, time to completion)

Attention Measures	DSF	DS/C
DSF	-	
DS/C	.26*	-
TMTA	-.46*	-.51*

Note. DSF = Digit Span Forward, DS/C = Digit Symbol Coding, TMTA = Trail Making Test Part A.

*p < .05

Table 19

Correlations among traditional neuropsychological executive functioning measures (N=72;
WAIS-III Digit Span, backward, total correct, Stroop Neuropsychological Screening Test, Color Word, time to completion, Paced Auditory Serial Addition Test, total correct)

Executive Functioning Measures	DSB	STRPCW
DSB	-	
STRPCW	-.38*	-
PASAT	.46*	-.40*

Note. DSB = Digit Span Backward, STRPCW = Stroop Neuropsychological Screening Test, Color Word, PASAT = Paced Auditory Serial Addition Test.

*p < .05

Table 20

Correlations among traditional neuropsychological memory measures (N=72; Ray Auditory
Verbal Learning Test total correct, WMS-III Verbal Paired Associates total correct, WAIS-III Digit Symbol Incidental Learning total correct)

Memory Measures	RAVLT	VPA
RAVLT	-	
VPA	.61*	-
DSIL	.49*	.35*

Note. RAVLT = Ray Auditory Verbal Learning Test, VPA = Verbal Paired Associates, DSIL = Digit Symbol Incidental Learning.

*p < .05

Table 21

Correlations among traditional neuropsychological visuospatial processing measures (N=72;
WAIS-III Matrix Reasoning total correct, WAIS-III Block Design total score, WMS-R Figural Memory total correct)

Visuospatial Processing Measures	MXRS	BD
MXRS	-	
BD	.67*	-
FM	.36*	.48*

Note. MXRS = Matrix Reasoning, BD = Block Design, FM = Figural Memory.

*p < .05

Table 22

Correlations of traditional neuropsychological measures across four domains (1 – 4) with WinSCAT computerized measures (CDLTP, RMTP, M2STP, MTHTP, CDDTP) (N=72)

	CDLTP	RMTP	M2STP	MTHTP	CDDTP
1. DSF	***.08***	.14	.25*	.26*	-.09
DS/C	***.61****	.44*	.41*	.21*	.44*
TMTA	***-.48****	-.31*	-.39*	-.10	-.39*
2. DSB	.26*	***.17***	.17	***.33****	.10
STRPCW	-.23*	***-.28****	-.31*	***-.33****	-.24*
PASAT	.34*	***.22****	.08	***.42****	.18
3. RAVLT	.45*	.16	.25*	.17	***.47****
VPA	.32*	.07	.07	.22*	***.21****
DSIL	.49*	.07	.16	.07	***.49****
4. MXRS	.41*	.29*	***.33****	.17	.29*
BD	.51*	.34*	***.52****	.11	.46*
FM	.43*	.13	***.36****	.13	.41*

Note. Expected relations between traditional and computerized measures are in shaded italicized bold font; CDLTP=Computerized code substitution learning throughput (TP) score, RMTP=Computerized running memory TP score, M2STP=Computerized match-to-sample TP score, MTHTP=Computerized math TP score, CDDTP=Computerized code substitution delayed memory TP score, 1=traditional neuropsychological attention domain measures, 2=traditional neuropsychological executive functioning domain measures, 3=traditional neuropsychological memory domain measures, 4=traditional neuropsychological visuospatial domain measures. The names of the specific traditional neuropsychological measures represented in this table have been explained in Tables 18 – 21.

*$p < .05$

Table 23a

Relationships of demographic variables, intellectual functioning measure (Shipley t-score), and motor performance task, dominant hand (Grooved Pegboard t-score) with WinSCAT computerized measure Code Substitution Learning throughput score (CDLTP)

	t-test		ANOVA		Pearson Correlation	
	t	P	F	P	r	P
1. Age	-	-	-	-	-.61	.05
Gender	.42	ns	-	-	-	-
Ethnicity	-.55	ns	-	-	-	-
Education	-	-	.09	ns	-	-
2. Shipley	-	-	-	-	.14	ns
3. Grooved Pegboard	-	-	-	-	.01	ns

Note. Age, Shipley, and Grooved Pegboard were all analyzed using bivariate correlations. Gender and Ethnicity were analyzed using an independent samples t-test (ethnicity was divided into Caucasian and all others combined). Education was analyzed using analysis of variance (ANOVA) using four groups (high school, some college, four-year degree, and post-bachelors).

Table 23b

Relationships of demographic variables, intellectual functioning measure (Shipley t-score), and motor performance task, dominant hand (Grooved Pegboard t-score) with WinSCAT computerized measure Running Memory throughput score (RMTP)

	t-test		ANOVA		Pearson Correlation	
	t	P	F	P	r	P
1. Age	-	-	-	-	-.37	.05
Gender	.74	ns	-	-	-	-
Ethnicity	.66	ns	-	-	-	-
Education	-	-	.42	ns	-	-
2. Shipley	-	-	-	-	.19	ns
3. Grooved Pegboard	-	-	-	-	.09	ns

Note. Age, Shipley, and Grooved Pegboard were all analyzed using bivariate correlations. Gender and Ethnicity were analyzed using an independent samples t-test (ethnicity was divided into Caucasian and all others combined). Education was analyzed using analysis of variance (ANOVA) using four groups (high school, some college, four-year degree, and post-bachelors).

Table 23c

Relationships of demographic variables, intellectual functioning measure (Shipley t-score), and motor performance task, dominant hand (Grooved Pegboard t-score) with WinSCAT computerized measure Mathematical processing throughput (MTHTP)

	t-test		ANOVA		Pearson Correlation	
	t	P	F	P	r	P
1. Age	-	-	-	-	.09	ns
Gender	-.65	ns	-	-	-	-
Ethnicity	.06	ns	-	-	-	-
Education	-	-	1.04	ns	-	-
2. Shipley	-	-	-	-	.40	.05
3. Grooved Pegboard	-	-	-	-	-.05	ns

Note. Age, Shipley, and Grooved Pegboard were all analyzed using bivariate correlations. Gender and Ethnicity were analyzed using an independent samples t-test (ethnicity was divided into Caucasian and all others combined). Education was analyzed using analysis of variance (ANOVA) using four groups (high school, some college, four-year degree, and post-bachelors).

Table 23d

Relationships of demographic variables, intellectual functioning measure (Shipley t-score), and motor performance task, dominant hand (Grooved Pegboard t-score) with WinSCAT computerized measure Match-to-Sample throughput score (M2STP)

	t-test		ANOVA		Pearson Correlation	
	t	P	F	P	r	P
1. Age	-	-	-	-	-.44	.05
Gender	1.33	ns	-	-	-	-
Ethnicity	.67	ns	-	-	-	-
Education	-	-	.47	ns	-	-
2. Shipley	-	-	-	-	.07	ns
3. Grooved Pegboard	-	-	-	-	.12	ns

Note. Age, Shipley, and Grooved Pegboard were all analyzed using bivariate correlations. Gender and Ethnicity were analyzed using an independent samples t-test (ethnicity was divided into Caucasian and all others combined). Education was analyzed using analysis of variance (ANOVA) using four groups (high school, some college, four-year degree, and post-bachelors).

Table 23e

Relationships of demographic variables, intellectual functioning measure (Shipley t-score), and motor performance task, dominant hand (Grooved Pegboard t-score) with WinSCAT computerized measure Code Substitution Delayed Memory throughput score (CDDTP)

	t-test		ANOVA		Pearson Correlation	
	t	P	F	P	r	P
1. Age	-	-	-	-	-.58	.05
Gender	-.41	ns	-	-	-	-
Ethnicity	-.74	ns	-	-	-	-
Education	-	-	.24	ns	-	-
2. Shipley	-	-	-	-	-.01	ns
3. Grooved Pegboard	-	-	-	-	.11	ns

Note. Age, Shipley, and Grooved Pegboard were all analyzed using bivariate correlations. Gender and Ethnicity were analyzed using an independent samples t-test (ethnicity was divided into Caucasian and all others combined). Education was analyzed using analysis of variance (ANOVA) using four groups (high school, some college, four-year degree, and post-bachelors).

Table 24

Three Block Hierarchical Linear Regression Model with Code Substitution Learning predicting an index score of Attention

Model and Variables	Unadjusted R^2	Adjusted R^2	R^2 Change	sr	**B**	***SE B***	β
(Block 1 – Demographic Variables)	.28*	.27*	.28*				
Age				-.53	-.03	.01	-.53*
(Block 2 – Intellectual Functioning)	.39*	.38*	.11*				
Shipley Score				.34	.05	.01	.36*
(Block 3 – Computerized Measure)	.40*	.37*	.01				
Code Substitution Learning				.08	.01	.01	.11

Notes. Final N = 72. sr = semi-partial correlation, the square of which describes the percent variance accounted for by each predictor after accounting for previously-entered control variables. **B** = beta coefficient, which indicates the standardized strength of the relationship between the predictor variable and outcome variable. ***SE B*** = standardized error of the beta value, which equals the error term for the beta. β = partial correlation, which describes the percent account for by each predictor without accounting for the inclusion of previous predictor variables.

*$p < .05$

Table 25

Three Block Hierarchical Linear Regression Model with Math Processing predicting an index score of Executive Functioning

Model and Variables	Unadjusted R^2	Adjusted R^2	R^2 Change	sr	**B**	***SE B***	β
(Block 1 – Demographic Variables)	.05	.04	.05				
Age				-.22	-.01	.01	-.22
(Block 2 – Intellectual Functioning)	.29*	.27*	.24*				
Shipley Score				.49	.07	.01	.52*
(Block 3 – Computerized Measure)	.39*	.37*	.10*				
Math Processing				.32	.05	.01	.35*

Notes. Final N = 72. sr = semi-partial correlation, the square of which describes the percent variance accounted for by each predictor after accounting for previously-entered control variables. **B** = beta coefficient, which indicates the standardized strength of the relationship between the predictor variable and outcome variable. ***SE B*** = standardized error of the beta value, which equals the error term for the beta. β = partial correlation, which describes the percent account for by each predictor without accounting for the inclusion of previous predictor variables.

*$p < .05$

Table 26

Three Block Hierarchical Linear Regression Model with Running Memory predicting an index score of Executive Functioning

Model and Variables	Unadjusted R^2	Adjusted R^2	R^2 Change	sr	**B**	***SE B***	β
(Block 1 – Demographic Variables)	.05	.04	.05				
Age				-.22	-.01	.01	-.22
(Block 2 – Intellectual Functioning)	.29*	.27*	.24*				
Shipley Score				.49	.07	.01	.52*
(Block 3 – Computerized Measure)	.29*	.26*	.00				
Running Memory				.05	.00	.01	.06

Notes. Final N = 72. sr = semi-partial correlation, the square of which describes the percent variance accounted for by each predictor after accounting for previously-entered control variables. **B** = beta coefficient, which indicates the standardized strength of the relationship between the predictor variable and outcome variable. ***SE B*** = standardized error of the beta value, which equals the error term for the beta. β = partial correlation, which describes the percent account for by each predictor without accounting for the inclusion of previous predictor variables.

*$p < .05$

Table 27

Three Block Hierarchical Linear Regression Model with Code Substitution Delayed Memory predicting an index score of Memory

Model and Variables	Unadjusted R^2	Adjusted R^2	R^2 Change	sr	**B**	***SE B***	β
(Block 1 – Demographic Variables)	.13*	.12*	.13*				
Age				-.36	-.02	.01	-.36*
(Block 2 – Intellectual Functioning)	.47*	.46*	.34*				
Shipley Score				.59	.08	.01	.62*
(Block 3 – Computerized Measure)	.52*	.50*	.04*				
Code Substitution Delayed Memory				.21	.01	.01	.26*

Notes. Final N = 72. sr = semi-partial correlation, the square of which describes the percent variance accounted for by each predictor after accounting for previously-entered control variables. **B** = beta coefficient, which indicates the standardized strength of the relationship between the predictor variable and outcome variable. ***SE B*** = standardized error of the beta value, which equals the error term for the beta. β = partial correlation, which describes the percent account for by each predictor without accounting for the inclusion of previous predictor variables.

*$p < .05$

Table 28

Three Block Hierarchical Linear Regression Model with Match-to-Sample predicting an index score of Visuospatial Processing

Model and Variables	Unadjusted R^2	Adjusted R^2	R^2 Change	sr	**B**	***SE B***	β
(Block 1 – Demographic Variables)	.24*	.22*	.24*				
Age				-.49	-.03	.01	-.49*
(Block 2 – Intellectual Functioning)	.56*	.55*	.33*				
Shipley Score				.57	.08	.01	.61*
(Block 3 – Computerized Measure)	.59*	.58*	.03*				
Match-to-Sample				.18	.02	.01	.20*

Notes. Final N = 72. sr = semi-partial correlation, the square of which describes the percent variance accounted for by each predictor after accounting for previously-entered control variables. **B** = beta coefficient, which indicates the standardized strength of the relationship between the predictor variable and outcome variable. ***SE B*** = standardized error of the beta value, which equals the error term for the beta. β = partial correlation, which describes the percent account for by each predictor without accounting for the inclusion of previous predictor variables.

*$p < .05$